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**(54) Title:** PEPTIDE ANALOGS

**(57) Abstract**

A genus of novel peptide analogs which have potent renin-inhibiting activity, methods of treating renin-based hypertension using these compounds, and pharmaceutical compositions containing these compounds as active ingredients.

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# PEPTIDE ANALOGS

## Technical Field

The present invention relates to novel organic compounds which inhibit renin, processes for making such compounds, synthetic intermediates employed in these processes and methods of treating hypertension with such compounds.

## Background Art

Renin is a proteolytic enzyme synthesized and stored principally in a specific part of the kidney called the juxtaglomerular apparatus. Any of three different physiologic circumstances may cause the release of renin into the circulation: (a) a decrease in the blood pressure entering or within the kidney itself; (b) a decrease in the blood volume in the body; or (c) a fall in the concentration of sodium in the distal tubules of the kidney.

When renin is released into the blood from the kidney, the renin-angiotensin system is activated, leading to vasoconstriction and conservation of sodium, both of which result in increased blood pressure. The renin acts on a circulating protein, angiotensinogen, to cleave out a fragment called angiotensin I (AI). AI itself has only slight pharmacologic activity but, after additional cleavage by a second enzyme, angiotensin converting enzyme (ACE), forms the potent molecule angiotensin II (AII). The major pharmacological effects of AII are vasoconstriction and stimulation of the adrenal cortex to release aldosterone, a hormone which causes sodium retention. AII is cleaved by an aminopeptidase to form angiotensin III (AIII), which compared to AII, is a less potent vasoconstrictor but a more potent inducer of aldosterone release.

Inhibitors of renin have been sought as agents for control of hypertension and as diagnostic agents for identification of cases of hypertension due to renin excess.

With these objectives in mind, the renin-angiotension system has been modulated or manipulated, in the past, with ACE inhibitors. However, ACE acts on several substrates other than angiotensin I (AI), most notably the kinins which cause such undesirable side effects as pain, "leaky" capillaries, prostaglandin release and a variety of behavioral and neurologic effects. Further, ACE inhibition leads to the accumulation of AI. Although AI has much less vasoconstrictor activity than AII, its presence may negate some of the hypotensive effects of the blockade of AII synthesis.

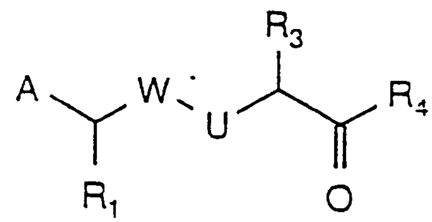
Inhibition of other targets in the renin-angiotensin system such as AII with compounds such as saralasin can block AII activity, but would leave unimpaired and perhaps enhance the hypertensive effects of AIII.

On the other hand, there are no known side effects which result when renin is inhibited from acting on its substrate. Considerable research efforts have thus been carried out to develop useful inhibitors of renin. Past research efforts have been directed to renin antibodies, pepstatin, phospholipids and substrate analogs such as tetrapeptides and octapeptides to tridecapeptides. These inhibitors either demonstrate poor activity in inhibiting renin production or poor specificity for inhibiting renin only. However, Boger et al., have reported that statine-containing peptides possess potent and specific renin-inhibiting activity (Nature. Vol. 303, p. 81, 1983). In addition, Szelke and co-workers have described polypeptide analogs containing a non-peptide link (Nature, Vol. 299, p. 555,

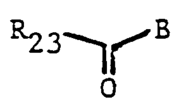
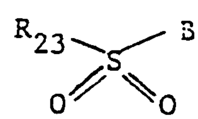
1982) which also cause potent renin inhibition and show a high specificity for this enzyme.

Disclosure of the Invention

In accordance with the present invention, there are renin inhibiting compounds of the formula:



wherein A is hydrogen; loweralkyl; arylalkyl; $OR_{20}$ or $SR_{20}$ wherein $R_{20}$ is hydrogen, loweralkyl or aminoalkyl; $NR_{21}R_{22}$ wherein $R_{21}$ and $R_{22}$ are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl;

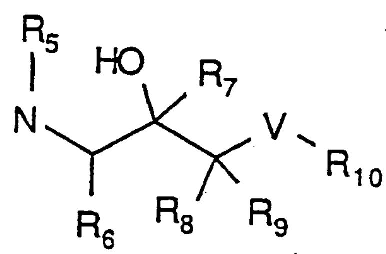
 and 

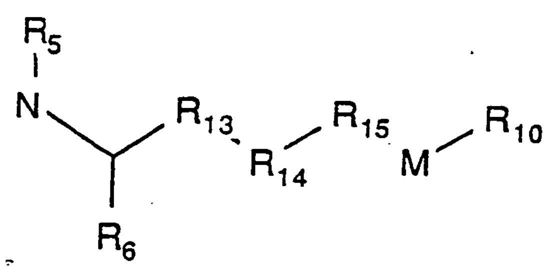
wherein B is NH, alkylamino, S, O, $CH_2$, $NHCH_2$ or CHOH and $R_{23}$ is loweralkyl, cycloalkyl, aryl, arylalkyl, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, [(dialkylamino)alkyl](alkyl)amino, (dihydroxyalkyl)(alkyl)amino, carboxyalkyl, aminoalkyl, N-protected aminoalkyl, alkylaminoalkyl, alkoxycarbonylalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl or a substituted or unsubstituted heterocyclic;

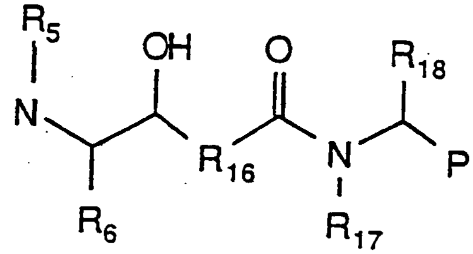
W is C=O or CHOH;

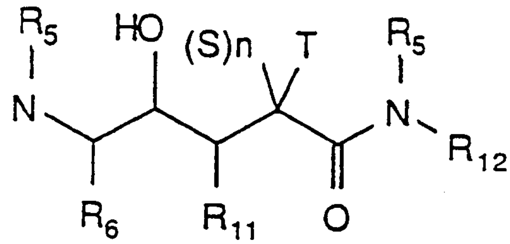
U is $CH_2$ or $NR_2$, provided that when W is CHOH then U is $CH_2$;

$R_1$ is loweralkyl, cycloalkylmethyl, benzyl, 4-methoxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazoyl)methyl, 4-hydroxybenzyl, $\alpha$,$\alpha$-dimethylbenzyl, 1-benzyloxyethyl, phenethyl, phenoxy, thiophenoxy or anilino; provided if $R_1$ is phenoxy, thiophenoxy or anilino, B is $CH_2$ or CHOH or A is hydrogen; $R_3$ is loweralkyl, loweralkenyl, [(alkoxy)alkoxy]loweralkyl, (thioalkoxy)alkyl, benzyl or heterocyclic ring substituted methyl; $R_4$ is

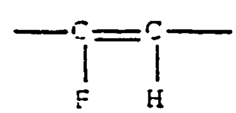








wherein $R_5$ is hydrogen or loweralkyl; $R_6$ is loweralkyl, cycloalkylmethyl, benzyl, or $CH_2R_{24}$, where $R_{24}$ is selected from 1,3-dioxan-2-yl; 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl or 1,3-dithian-2-yl; $R_7$, $R_8$ and $R_9$ are hydrogen or loweralkyl and may be the same or different; V is NH, O, S, SO, $SO_2$, or $CH_2$; $R_{10}$ is loweralkyl, cycloalkyl, cycloalkyl-alkyl, aryl, arylalkyl or an N-protecting group, or V and $R_{10}$ taken together are $N_3$; with the proviso that $R_{10}$ may be an N-protecting group only when V is NH; $R_{13}$ is CHOH or CO; $R_{14}$ is $CH_2$, $CF_2$ or CF with the proviso that when $R_{13}$ is CO, $R_{14}$ is $CF_2$; $R_{15}$ is $CH_2$, $CHR_{25}$ wherein $R_{25}$ is loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, or $R_{14}$ and $R_{15}$ taken together can be



with the proviso that when $R_{14}$ is $CF_2$, $R_{15}$ is $CH_2$; M is O, S, SO, $SO_2$, $NR_{26}$ wherein $R_{26}$ is hydrogen or loweralkyl, $NR_{27}SO_2$ or $NR_{27}CO$ wherein $R_{27}$ is hydrogen or loweralkyl, or M and $R_{10}$ taken together are $N_3$; $R_{16}$ is $CH_2$, $CF_2$ or $CHR_{45}$ where $R_{45}$ is loweralkyl, hydroxy, hydroxyalkyl,

alkoxy, allyl, alkaryloxy or thioalkyl $R_{17}$ is hydrogen or loweralkyl; $R_{18}$ is loweralkyl or lipophilic or aromatic amino acid side chains; P is hydrogen, loweralkyl or $-CH_2OR_{28}$, wherein $R_{28}$ is hydrogen, loweralkyl or alkaryl; $R_{11}$ is hydrogen or hydroxy; n is 0 or 1; when n is 0, T is alkylidene or alkylidene oxide; when n is 1, S is hydrogen or hydroxy and T is loweralkyl, hydroxyalkyl, aminoalkyl, haloalkyl, or azidoalkyl; $R_{19}$ is hydrogen or loweralkyl; $R_{12}$ is hydrogen, loweralkyl, alkyl- cycloalkyl, arylalkyl, aminoalkyl, dialkylaminoalkyl; and pharmaceutically acceptable salts thereof.

The chiral centers of the compounds of the invention may have either the "R" or "S" configuration but preferably have an "S" configuration except where noted. The terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect nitrogen atoms against undesirable reactions during synthetic procedures or to prevent the attack of exopeptidases on the final compounds or to increase the solubility of the final compounds and includes but is not limited to acyl, acetyl, pivaloyl, t-butylacetyl, t-butyloxycarbonyl(Boc), benzyloxycarbonyl (Cbz) or benzoyl groups or an L- or D-aminoacyl residue, which may itself by N-protected similarly.

The term "loweralkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 7 carbon atoms including but not limited to methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, 2-methylhexyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "arylalkyl" as used herein refers to an unsubstituted or substituted aromatic ring appended to an alkyl radical including but not limited to benzyl, 1- and 2-naphthylmethyl, halobenzyl and alkoxybenzyl.

The term "alkylamino" as used herein refers to a loweralkkyl radical appended to an NH radical.

The term "cycloalkyl" as used herein refers to an aliphatic ring having 4 to 7 carbon atoms.

The term "cycloalkylmethyl" as used herein refers to a cycloalkyl group appended to a methyl radical, including but not limited to cyclohexylmethyl.

The term "aryl" as used herein refers to a substituted or unsubstituted aromatic ring including but not limited to phenyl, naphthyl, halophenyl and alkoxyphenyl.

The term carboxyalkyl as used herein refers to a carboxylic acid group (-COOH) appended to a loweralkyl radical.

The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{29}O-$ and $R_{29}S-$, respectively, wherein $R_{29}$ is a loweralkyl group.

The term "arylalkoxy" as used herein refers to an aryl appended to an alkoxy radical.

The term "arylalkoxyalkyl" as used herein refers to an aryalkoxy appended to a loweralkyl radical.

The term "dialkylamino" as used herein refers to $-NR_{30}R_{31}$ wherein $R_{30}$ and $R_{31}$ are independently selected from loweralkyl groups.

The term "N-protected aminoalkyl" as used herein refers to $NHR_{32}$ is appended to a loweralkyl group, where $R_{32}$ is an N-protecting group.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group appended to a loweralkyl radical, including but not limited to imidazoylalkyl.

The term alkoxycarbonylalkyl as used herein refers to $R_{33}C{=}OR_{34}$, wherein $R_{33}$ is an alkoxy

group and $R_{34}$ is loweralkyl.

The terms "alkenyl" and "alkenyloxy", as used herein refer to $R_{35}$- and $R_{35}O$-, respectively wherein $R_{35}$ is an unsaturated alkyl group.

The term "hydroxyalkoxy" as used herein refers to -OH appended to alkoxy radical.

The term "dihydroxyalkoxy" as used herein refers to an alkoxy radical which is disubstituted with -OH radicals.

The term "(hydroxyalkyl)(alkyl)amino" as used herein refers to $-NR_{36}R_{37}$ wherein $R_{36}$ is hydroxyalkyl and $R_{37}$ is loweralkyl.

The term "(dihydroxyalkyl)(alkyl)amino" as used herein refers to $-NR_{38}R_{39}$ wherein $R_{38}$ is dihydroxyalkyl and $R_{39}$ is loweralkyl.

The term "dihydroxyalkyl" as used herein refers to a loweralkyl radical which is disubstituted with -OH radicals.

The term "((dialkylamino)alkyl)(alkyl)amino" as used herein refers to $-NR_{40}R_{41}$ wherein $R_{40}$ is an alkyl radical which is substituted with a dialkylamino radical and $R_{41}$ is loweralkyl.

The term "carboalkoxyalkyl" as used herein refers to a loweralkyl radical which is substituted at any position with one or more carboalkoxy groups and includes but is not limited to carboalkoxymethyl, carboalkoxyethyl, carboalkoxypropyl, carboalkoxybutyl and carboalkoxypentyl.

The term "carboalkoxy group" as used herein refers to an acyl radical which has appended to it an alkoxy group and includes but is not limited to methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, isopropyloxycarbonyl, butyloxycarbonyl, isobutyloxycarbonyl and t-butyloxycarbonyl.

The term "alkylaminoalkyl" as used herein refers to $NHR_{42}$ appended to a loweralkyl radical,

wherein $R_{42}$ is a loweralkyl group.

The term "(N-protected)(alkyl)aminoalkyl" as used herein refers to $NR_{32}R_{42}$, which is appended to a loweralkyl radical, wherein $R_{32}$ and $R_{42}$ are as defined above.

The term "dialkylaminoalkyl" as used herein refers to $NR_{43}R_{44}$ appended to a loweralkyl radical wherein $R_{43}$ and $R_{44}$ are independently selected from loweralkyl.

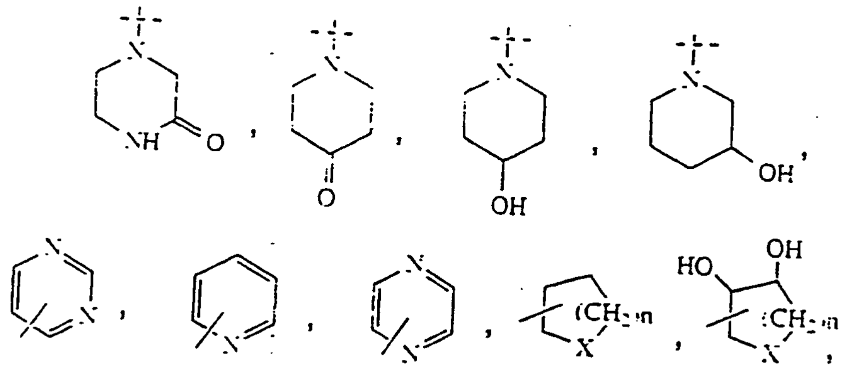
The term "(thioalkoxy)alkyl" as used herein refers to thioalkoxy appended to a loweralkyl radical.

The term "aminoalkyl" as used herein refers to $-NH_2$ appended to a loweralkyl radical.

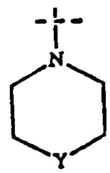
The term "heterocyclic ring" or "heterocyclic" as used herein refers to any 5-, 6-, 9- or 10-membered ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; having various degrees of unsaturation; wherein the nitrogen and sulfur heteroatoms may optionally be quaternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring. Heterocyclics in which nitrogen is the heteroatom are preferred. Fully saturated heterocyclics are also preferred. Preferred heterocyclics are: pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiazolidinyl, thiazolyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl and benzothienyl.

Saturated heterocyclics may be unsubtituted or mono- or di-substituted with hydroxy, oxo, amino, alkylamino, dialkylamino or loweralkyl. Unsaturated heterocyclics may be unsubstituted or monosubstituted with hydroxy, amino, alkylamino, dialkylamino or loweralkyl.

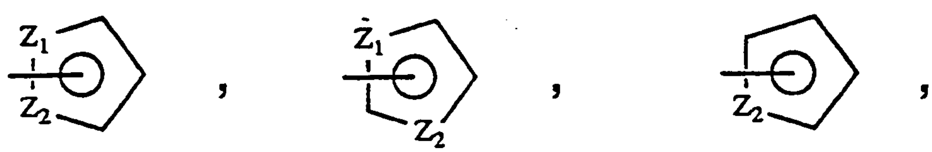
The most preferred heterocyclics are as follows:



wherein n is 1 or 2 and X is N, NH, O, S, provided that X is the point of connection only when X is N,



wherein Y is NH, N-loweralkyl, O, S, or $SO_2$, or



wherein $Z_1$ is N, O, or S and not the point of connection and $Z_2$ is N when it is the point of connection and NH, O or S when it is not the point of connection.

The terms "lipophilic or aromatic amino acid side chains" as used herein refers to those amino acid side chains which have an affinity for lipids or have an aromatic ring and include but are not limited to benzyl, isobutyl, isopropyl, sec-butyl, imidazol-4-yl- methyl, p-hydroxybenzyl, 1- and 2-naphthylmethyl, (pyrazolyl)-methyl, (thiazolyl)methyl, and cyclohexylmethyl. The

term "hydrophilic, amino acid side chain" as used herein refers to those amino acid side chains which have an affinity for water and include but are not limited to, those of serine, threonine, allothreonine, homoserine, cysteine, ornithine, arginine, and glutamine. General reference to amino acid side chains in both the description and claims herein is to be taken as reference to such, whether naturally occurring in protein or not, and to both D- and L-forms.

The term "alkylidene" used herein refers to a straight or branched chain alkyl radical which is attached via a carbon-carbon double bond and includes but is not limited to methylidene, ethylidene, 1-propylidene, 1-butylidene, 1-pentylidene, 2-propylidene, 2-butylidene, 2-pentylidene, 3-pentylidene, 3-hexylidene, 3-heptylidene, and 4-heptylidene.

The term "alkylidene oxide" used herein refers to an epoxide moiety which is derived from an alkylidene group.

The terms "thioalkyl, haloalkyl or azidoalkyl" used herein refer to an alkyl radical which has appended to it a thio, halo or azido radical, respectively.

The terms "Ala", "His", "Leu", "Phe", "Tyr", "Cys", "Gly", "Lys", Sar", "Ser", "Thr" and "Pro" as used herein refer to alanine, histidine, leucine, phenylalanine, tyrosine, cysteine, glycine, lysine, sarcosine, serine, threonine, and proline, respectively.

The following examples will serve to further illustrate preparation of novel compounds of the present invention.

Example 1

(3S,4S)-4-t-Butyloxycarbonylamino-3-hydroxy-6-methyl-1-heptene

To a rapidly stirred -78°C solution of Boc-leucinal (1.5 g, 6.97 mmol) in anhydrous tetrahydrofuran (THF) (10 mL) was added a -78°C solution of vinyl

magnesium bromide (7 mmol) in anhydrous THF (40 mL) dropwise over the course of 15 min; 2 h later the mixture was acidified to pH 7. The organic phase was separated, washed with brine (2 x 10 mL) and dried ($Na_2SO_4$). Filtration and evaporation provided an oil which was purified by flash chromatography on silica gel with 7/3 hexane-ether. There was obtained 3.9 (53%) of product, m.p. 57-59°C.

Anal. calcd. for $C_{13}H_{25}NO_3$: C, 64.17; H, 10.36; N, 5.76.

Found: C, 64.19; H, 10.13; N, 5.66.

Example 2

4(S)-Isobutyl-5(S)-vinyl-2-oxazolidinone

To a solution of (3S,4S)-4-t-butyloxycarbonylamino-3-hydroxy-6-methyl-1-heptane (10.5 g, 0.043 mol) in dimethylformamide (DMF) (100 mL) was added sodium hydride (2.4 g of 50% dispersion) portionwise at 0-5°C. After stirring for 20 h at room temperature, the reaction mixture was poured into cold aqueous NaCl solution. The resulting mixture was extracted with methylene chloride and the organic phase was washed several times with brine solution. Drying over $MgSO_4$ and evaporation gave a residue which was flash chromatographed on silica gel eluting with hexane/ethyl acetate mixtures. There was obtained 5.7 g (78%) of the desired compound as an oil. NMR (300 MHz, $CDCl_3$, ppm): 0.9 (2d,6H), 1.35-1.75 (m,3H), 3.6 (m,1H), 4.55 (t,1H), 5.4 (m,2H), 5.9 (m,1H).

Example 3

4(S)-Isobutyl-5(S)-(2-mesyloxyethyl)-2-oxazolidinone

To a 0°C solution of 4(S)-isobutyl-5(S)-vinyl-2-oxazolidinone (4.7 g, 0.028 mol) in THF (20 mL) was added 9-BBN [9-borabicyclo-(3.3.1)nonane, 75 mL, 0.0375 mol in THF] by dropwise addition. After stirring for 5 h at room temperature, the reaction was quenched by the addition of water (1 mL). A solution of NaOH

(6.7 g) in water, (21 mL) was then added followed by careful addition of $H_2O_2$ (18 mL of 30%). The resulting mixture was heated at 65°C for 1 h, the THF was partially evaporated and the residue was distributed between ethyl acetate and brine solution. The organic phase was washed with brine solution and dried over $MgSO_4$. Evaporation of the solvent gave a residual oil which was flash chromatographed on silica gel eluting with 5% MeOH in methylene chloride. The pure fractions were combined and evaporated to give 4.62 g of 4(S)-isobutyl-5(S)-(2-hydroxyethyl)-2-oxazolidinone. A solution of this material (3.95 g, 0.021 mol) and triethylamine (3.2 g, 0.032 mol) in methylene chloride (40 mL) was cooled to 0°C and treated by dropwise addition with mesyl chloride (2.89 g, 0.025 mol). After stirring for 1 h at 0-5°C, the methylene chloride was washed successively with 0.5 N HCl, aqueous $NaHCO_3$ and brine solution. The organic solution was dried and evaporated to a solid product. Recrystallization from hexane/ methylene chloride gave 3.9 g (70%) of product, m.p. 99-100°C.

Anal. calcd. for $C_{10}H_{19}NO_5S$: C, 45.27; H, 7.22; N, 5.28.

Found: C, 45.38; H, 7.18; N, 5.23.

## Example 4

## 4(S)-Isobutyl-5(S)-[2-(phenethylmercapto)ethyl]-2-oxazolidinone

To a 0°C solution of 4(S)-isobutyl-5(S)-(2-mesyloxyethyl)-2-oxazolidinone (500 mg, 1.88 mmol) and phenethyl mercaptan (273 mg, 1.98 mmol) in THF (6 mL) was added NaH (95 mg, 1.98 mmol of a 50% dispersion) all at once. The reaction was stirred for 3 h at room temperature and then distributed between methylene chloride and brine solution. The organic layer was washed with brine solution, dried over $MgSO_4$ and evaporated. The residue was chromatographed on

silica gel eluting with 65/35 hexane/ethyl acetate to give 570 mg (98%) of product as an oil.

Anal. calcd. for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56.

Found: C, 66.60; H, 8.32; N, 4.58.

Example 5

4(S)-Isobutyl-5(S)-[2-(isoamylmercapto)ethyl]-2-oxazolidinone

Using the procedure of Example 4 but changing phenethyl mercaptan to isoamyl mercaptan, gave the desired compound in 95% yield.

Anal. calcd. for $C_{14}H_{27}NO_2S$: C, 61.50; H, 9.95; N, 5.12.

Found: C, 61.19; H, 10.02; N, 5.00.

Example 6

4(S)-Isobutyl-5(S)-[2-(isobutylmercapto)ethyl]-2-oxazolidinone

Using the procedure of Example 4 but changing phenethyl mercaptan to isobutyl mercaptan, gave the desired compound in 96% yield.

Example 7

4(S)-Isobutyl-5(S)-[2-(isopropylmercapto)ethyl]-2-oxazolidinone

Using the procedure of Example 4 but changing phenethyl mercaptan to isopropyl mercaptan, gave the desired compound in 93% yield.

Example 8

4(S)-Isobutyl-5(S)-[2-(phenethylsulfonyl)ethyl]-2-oxazolidinone

To a solution of 4(S)-isobutyl-5(S)-[2-(phenethylmercapto)-ethyl]-2-oxazolidinone (0.49 g, 1.59 mmol) in methylene chloride (6 mL) was added 0.756 g (3.5 mmol) of m-chloroperoxybenzoic acid. After stirring for 1 h at room temperature, the methylene chloride solution was washed successively with aqueous $NaHSO_3$ and aqueous NaOH. The organic layer was dried

and evaporated to a solid product. Trituration with hexane/ether (50/50) gave 495 mg (92%) of product, m.p. 100-101°C.

Anal. calcd. for $C_{17}H_{25}NO_4S$: C, 60.15; H, 7.42; N, 4.13.

Found: C, 60.27; H, 7.42; N, 4.00.

Example 9

4(S)-Isobutyl-5(S)-[2-isoamylsulfonyl)ethyl]-2-oxazolidinone

Using the procedure of Example 8 with the resultant compound of Example 5, gave the desired compound, m.p. 87-88°C.

Anal. calcd. for $C_{14}H_{27}NO_4S$: C, 55.05; H, 8.91; N, 4.59.

Found: C, 55.11; H, 9.31; N, 4.61.

Example 10

(3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylmercaptoheptane

A solution of 4(S)-isobutyl-5(S)-[2-(phenethylmercapto)ethyl]-2-oxazolidinone (0.52 g, 1.69 mmol) and barium hydroxide octahydrate (1.06 g, 3.38 mmol) in dioxane (60 mL) and water (40 mL) was heated at reflux under $N_2$ for 21 h. The solid barium carbonate was filtered and the filtrate was partially evaporated. The residue was diluted with water and the resulting solution was extracted with ether. The organic extract was washed with brine solution, dried over $MgSO_4$ and evaporated to a residue. Trituration with cold hexane gave 365 mg (77%) of product, m.p. 95-96°C.

Anal. calcd. for $C_{16}H_{27}NOS$: C, 68.28; H, 9.67; N, 4.98.

Found: C, 67.99; H, 9.66; N, 4.75.

Example 11

(3S,4S)-4-Amino-3-hydroxy-1-isoamylmercapto-6-methylheptane

Using the procedure of Example 10 with the

resultant compound of Example 5, gave the desired compound, m.p. 64-65°C.

Anal. calcd. for $C_{13}H_{29}NOS$: C, 63.10; H, 11.81; N, 5.66.

Found: C, 63.34; H, 12.09; H, 5.50.

Example 12

(3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

Using the procedure of Example 10 with the resultant compound of Example 8, gave the desired compound, m.p. 153-154°C.

Anal. calcd. for $C_{16}H_{27}NO_3S \cdot H_2O$: C, 61.31; H, 8.68; N, 4.47.

Found: C, 60.66; H, 8.63; N, 4.19.

Example 13

(3S,4S)-4-Amino-3-hydroxy-1-isoamylsulfonyl-6-methylheptane

Using the procedure of Example 10 with the resultant compound of Example 9, gave the desired compound, m.p. 125-126°C.

Anal. calcd. for $C_{13}H_{29}NO_3S$: C, 55.88; H, 10.46; N, 5.01.

Found: C, 55.75; H, 10.52; N, 4.65.

Example 14

4(S)-Isobutyl-5(S)-(2-phenoxyethyl)-2-oxazolidinone

Using the procedure of Example 4 but changing phenethyl mercaptan to phenol and THF to DMF gave the desired compound in 54% yield.

Mass spectrum: $M^+ = 264$.

Example 15

(3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenoxyheptane

Using the procedure of Example 10 with the resultant compound of Example 14, gave the desired compound as an oil in 82% yield. Mass spectrum: $M^+ = 238$.

## Example 16

### Boc-Phe-Ala Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylmercaptoheptane

To a stirred -12°C solution of Boc-Phe-Ala-OH (47.8 mg, 0.142 mmol) in anhyrous tetrahydrofuran (3 mL) were added N-methylmorpholine (15.6 uL, 0.142 mmol) and isobutylchloroformate (18.4 uL, 0.142 mmol) sequentially. After 3 min, a -12°C solution of the resultant compound of Example 10 (0.142 mmol) in anhydrous tetrahydrofuran (2 mL) was added. Ten minutes later, the mixture was allowed to warm to room temperature for 2 h, at which time the solvent was evaporated, and the resulting residue was partitioned between ethyl acetate (20 mL) and saturated $NaHCO_3$ (5 mL). The organic phase was washed sequentially with 0.01 M $H_3PO_4$ (3 mL) and brine (5 mL). Drying ($Na_2SO_4$) and evaporating provided 77 mg (90%) of the desired compound as a glass.

Anal. calcd. for $C_{33}H_{49}N_3O_5S$: C, 66.08; H, 8.23; N, 7.00.

Found: C, 66.11; H, 8.35; H, 6.84.

## Example 17

### Boc-Phe-Ala Amide of (3S,4S)-4-Amino-3-hydroxy-1-isoamylmercapto-6-methylheptane

Using the procedure of Example 16 with the resultant compound of Example 11, gave the desired compound, m.p. 137-138°C.

Anal. calcd. for $C_{30}H_{51}N_3O_5S$: C, 63.68; H, 9.09; N, 7.43.

Found: C, 64.01; H, 8.93; N, 7.39.

## Example 18

### Boc-Phe-Ala Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

Using the procedure of Example 8 with the resultant compound of Example 16, gave the desired compound, m.p. 186-187°C.

Anal. calcd. for $C_{33}H_{49}N_3O_7S$: C, 62.74; H, 7.82; N, 6.65.

Found: C, 62.67; H, 7.56; N, 6.61.

Example 19

Boc-Phe-Ala Amide of (3S,4S)-4-Amino-3-hydroxy-1-isoamylsulfonyl-6-methylheptane

Using the procedure of Example 8 with the resultant compound of Example 17, gave the desired compound.

Anal. calcd. for $C_{30}H_{51}N_3O_7S$: C, 60.27; H, 8.60; N, 7.03.

Found: C, 60.47; H, 8.29; N, 6.98.

Example 20

Boc-Phe-Ala Amide of (3S,4S)-4-Amino-3-hydroxy-1-isoamylfulfonyl-6-methylheptane

Using the procedure of Example 8 but using only one molar equivalent of m-chloroperoxybenzoic acid and conducting the reaction at 0°C, the resultant compound from Example 17 was converted to the desired compound.

Example 21

Boc-Phe-Ala Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenoxyheptane

Using the procedure of Example 16 with the resultant compound from Example 15, gave the desired compound.

Example 22

Boc-Phe-His Amide of (3S,4S)-4-Amino-3-hydroxy-1-isoamylsulfonyl-6-methylheptane

To a stirred -23°C solution of Boc-Phe-His-OH (153 mg, 0.38 mmol) in anhydrous dimethylformamide (5 mL) was added a solution of the compound from Example 13 (0.38 mmol) in dimethylformamide (3 mL). Hydroxybenzotriazole (HOBT, 77 mg, 0.57 mmol) and dicyclohexylcarbodiimide (DDC, 78 mg, 0.38 mmol) were then added sequentially. After 2.5 h the mixture was warmed to 25°C, stirred 12 h, filtered and evaporated to a

residue which was partitioned between ethyl acetate (20 mL) and saturated $NaHCO_3$ (8 mL). The organic phase was then washed separately with saturated $NaHCO_3$ (8 mL) and brine (8 mL). Drying ($Na_2SO_4$) and evaporating provided a white solid which was chromatographed on $SiO_2$ (95/5, dichloromethane/ methanol) to give 180 mg (75%) of the desired compound. Mass spectrum: $(M+H)^+ = 664$.

## Example 23

## Boc-Phe-His Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

Using the procedure of Example 22 with the resultant compound of Example 12, gave the desired compound.

Anal. calcd. for $C_{36}H_{51}N_5O_7S$: C, 61.96; H, 7.37; N, 10.03.

Found: C, 61.38; H, 7.71; N, 9.07.

## Example 24

## (5S,6S)-5-Acetoxy-6-t-butyloxycarbonylamino-8-methyl-1-nonene

Using the procedure of Example 1 but changing vinyl magnesium bromide to butenyl magnesium bromide, gave a 56% yield of (5S,6S)-6-t-butyloxycarbonylamino-5-hydroxy-8-methyl-1-nonene as an oil. A 25 g (0.092 mol) sample of this material was dissolved in methylene chloride (200 mL) containing 10 mL of pyridine. Acetic anhydride (11.74 g, 0.115 mol) was added by dropwise addition and the resulting mixture was stirred for 24 h at room temperature. The mixture was washed successively with aqueous $NaHCO_3$, aqueous citric acid and brine solution. After drying over $MgSO_4$, the solvent was evaporated to a residue. Flash chromatography on silica gel gave an 82% yield of product as an oil.

Anal. calcd. for $C_{17}H_{31}NO_4$: C, 65.15; H, 9.97; N, 4.47.

Found: C, 65.11; H, 9.66; N, 4.30.

Example 25

4(S)-Isobutyl-5(S)-(4-butenyl)-2-oxazolidinone

A solution of the compound from Example 24 (33 g, 0.105 mol) dissolved in 150 mL of dimethylformamide and 50 mL of tetrahydrofuran was treated with 11 g (0.204 mol) of sodium methoxide in one portion.
The reaction mixture was stirred overnight at room temperature and then poured into an acidified solution of aqueous NaCl with cooling. The resulting mixture was extracted with ether. The ethereal extract was washed three times with brine solution and dried over $MgSO_4$. Evaporation of the solvent gave 19.6 g (95%) of liquid product.

Anal. calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10.

Found: C, 67.25; H, 9.84; H, 6.91.

Example 26

4(S)-Isobutyl-5(S)-(2-formylethyl)-2-oxazolidinone

To a stirred solution of the compound from Example 25 (5.0 g, 25.2 mmol) in dichloromethane (60 mL) was added m-chloroperbenzoic acid (MCPBA, 10.8 g of 80% MCPBA, 50 mmol). After 68 h the reaction mixture was cooled to 0°C, and 0°C 10% $Na_2SO_3$ was added with stirring. After 15 min, the solid was filtered off and extracted with dichloromethane. The combined organic phase was washed sequentially with 0°C 10% $Na_2SO_3$, saturated $NaHCO_4$ and water. Drying ($MgSO_4$), filtering and evaporating provided crude epoxide which was chromatographed on silica gel eluting with 50/50 hexane-ethyl acetate to give a 73% yield of purified epoxide. A 10 g (0.047 mol) sample of the above epoxide was mixed with 200 mL of 6% perchloric acid and kept for 24 h at room temperature. The solution was neutralized with solid sodium bicarbonate, saturated with sodium chloride and extracted with ethyl acetate. Evaporation

of the solvent left 10 g of glycolic material as a viscous syrup. The above glycol (10 g, 0.043 mol) was dissolved in 150 mL of water and treated all at once with a solution of periodic acid (9.1 g, 0.04 mol) in 150 mL of water. After stirring at 25°C for 5 h, the mixture was extracted with methylene chloride. The dried methylene chloride solution was evaporated to give a quantitative yield of product.

## Example 27

### 4(S)-Isobutyl-5(S)-(6-methyl-3-oxoheptyl)-2-oxazolidinone

A 2 g (0.01 mol) portion of the compound from Example 26 was dissolved in THF (50 mL) and treated at 0-5°C with 37.5 mL of an 0.8 M solution of isopentyl magnesium bromide in THF. The reaction was stirred for 2 h at room temperature and then poured into ice water which contained 6.5 mL of 6 N HCl. The mixture was extracted with methylene chloride. Evaporation of the dried methylene chloride solution gave a quantitative yield of the Grignard adduct. This material was dissolved in 300 mL of acetone and treated by dropwise addition with Jones solution until the orange color persisted. The chromium salts were filtered and the filtrate was evaporated. The residue was diluted with ether and the resulting solution was washed successively with aqueous $NaHCO_3$ and brine solution. After drying over $MgSO_4$, the solvent was evaporated to give 1.7 g (66%) of product as an oil. NMR (300 MHz, $CDCl_3$, ppm): 0.86-0.96 (m,12H), 2.41 (m,2H), 2.67 (m,2H), 3.5 (m,1H), 4.15 (m,1H).

## Example 28

### 4(S)-Isobutyl-5(S)-(6-methyl-3-oxoheptyl)-2-oxazolidinone Ethylene Ketal

A mixture of the product from Example 27 (2.5 g, 9.3 mmol), ethylene glycol (7.5 mL) and p-toluenesulfonic acid (60 mg) in toluene (100 mL) was

heated at reflux with a Dean-Stark trap for 8 h. The cooled mixture was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was flash chromatographed on silica gel eluting with 65/35 hexane-ethyl acetate to give 2.3 g (79%) of product. NMR (300 MHz, $CDCl_3$, ppm): 0.85-0.95 (4d,12H), 3.5 (m,1H), 3.95 (s,4H), 4.15 (m,1H).

Example 29

(4S,5S)-4-Amino-2,11-dimethyl-5-hydroxy-8-oxododecane Ethylene Ketal

Using the procedure of Example 10 with the resultant compound of Example 28, gave the desired compound in 73% yield, m.p. 26°C.

Example 30

Boc-Phe-Ala Amide of (4S,5S)-4-Amino-2,11-dimethyl-5-hydroxy-8-oxododecane

Using the procedure of Example 16 with the resultant compound of Example 29, gave a 90% yield of the title compound as the corresponding ethylene ketal.

Anal. calcd. for $C_{33}H_{55}N_3O_7$: C, 65.43; H, 9.15; N, 6.94.

Found: C, 65.28; H, 9.16; N, 6.67.

The desired deketalized product was obtained as follows. A solution of the ketal (400 mg) was stirred for 24 h in 37 mL acetic acid/water/tetrahydrofuran (3/1/1). The solvents were evaporated under reduced pressure and the residue was triturated with hexane-ether (65:35) to give 280 mg (76%) of product; m.p. 137-138°C.

Anal. calcd. for $C_{31}H_{51}N_3O_6$: C, 66.28; H, 9.15; N, 7.48.

Found: C, 66.29; H, 9.23; N, 7.32.

Example 31

Boc-His Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

Using the procedure of Example 22 with the resultant compound of Example 12 and Boc-His-OH rather than Boc-Phe-His-OH, gave the desired compound.

Example 32

[(4-Morpholinyl)carbonyl]-Phe Methyl Ester

A suspension of L-phenylalanine methyl ester hydrochloride (6 g) in toluene (125 mL) was heated to 100°C while phosgene gas was bubbled into the reaction mixture. After approximately 1.5-2 h, the mixture became homogeneous. The passage of phosgene was continued for an additional 15 min, keeping the temperature at 90-100°C. The toluene was then evaporated and the residue chased several times with benzene. A 6.5 g (0.03167 mol) sample of -isocyanato-L-phenylalanine methyl ester was dissolved in 50 mL of methylene chloride and cooled to 0°C. Morpholine (2.76 mL, 0.03167 mol) dissolved in 5 mL of methylene chloride was added dropwise. After 10 min at 0-5°C, the reaction mixture was distributed between 0.5 N HCl and methylene chloride. The organic layer was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent gave 7 g of product after trituration with hexane, m.p. 90-91°C.

Example 33

[(4-Morpholinyl)carbonyl]-Phe-OH

To a 0°C solution of the product from Example 32 (3.63 mmol) in dioxane (15 mL) was added a solution of lithium hydroxide (0.174 g, 4.15 mmol) in water (7.5 mL). After stirring for 1 h at 0-5°C, the reaction mixture was diluted with cold water and extracted 2X with ether. The aqueous portion was acidified with 6N HCl and extracted with ether. The organic extract was washed with brine and evaporated to

give an 87% yield of product as a viscous liquid.

Example 34

Boc-(Me)His Amide of (3S,4S)-4-Amino-
3-hydroxy-6-methyl-1-phenethylsulfonyl Heptane

To a stirred solution of N -(t-butyloxycarbonyl)-N -methyl-$N^{im}$-tosyl-L-histidine [J. Med. Chem. 29, 2088 (1986), 9.15 mmol] and the product from Example 12 (6.1 mmol) in dichloromethane (75 mL) was added 1.28 mL (9.18 mmol) of triethylamine, followed by the slow addition of diethoxyphosphoryl cyanide (1.36 mL, 8.87 mmol). After being stirred at room temperature for 16 h, the reaction mixture was diluted with dichloromethane and then washed with saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and then concentrated. The residue was chromatographed on silica gel eluting with ethyl acetate/hexane mixture to give a 75% yield of coupled product.

The above product was stirred in $CH_3OH$ with 5 equiv. HOBT for 16 h. The reaction mixture was filtered. The filtrate was evaporated to solid which was taken up with $CHCl_3$, washed with dil $NaHCO_3$, brine, dried and filtered. The resultant residue after evaporation was chromatographed eluting with 5% $CH_3OH/CHCl_3$. The desired product was obtained in 60% yield.

Example 35

[(4-Morpholinyl)carbonyl]-Phe-(Me)His
Amide of (3S,4S)-4-Amino-3-hydroxy-
6-methyl-1-phenethylsulfonylheptane

The product from Example 34 was deprotected with trifluoroacetic acid/methylene chloride (1:1) and the resultant amine coupled to the product from Example 33 using the method of Example 34. There was obtained a 50% yield of the title compound.

## Example 36

## 3-Benzyloxycarbonylamino-3-methylbutanoic Acid

A solution of 2,2-dimethyl-3-carbomethyoxy-propionic acid [LeMaul, Bull. Soc. Chim. Fr., 828 (1965), 20 g, 0.125 mol], diphenylphosphorylazide (34.3 g, 0.125 mol) and triethylamine was heated in toluene (150 mL) at 100°C for 2 h. After cooling to 5°C, the toluene solution was washed successively with 0.5 M HCl, aqueous $NaHCO_3$ and brine. Evaporation of the dried solution gave a residue which was chromatographed on silica gel eluting with 60/40 hexane/ether. There was obtained 13 g of methyl 3-isocyanato-3-methylbutanoate as a mobile liquid. A solution of this material in toluene (20 mL) was treated with benzyl alcohol (13 mL) and the resulting mixture heated at reflux for 40 h. Evaporation of the toluene left a residue which was dissolved in methanol (125 mL) and then treated with a solution of NaOH (6.6 g, 0.165 mol) in 22 mL of water. After 5 h, the reaction mixture was partially evaporated, washed with ether and acidified with 6N HCl. Extraction with methylene chloride and evaporation gave 21 g of the desired product. NMR (300 MHz, $CDCl_3$): 1.42 (s,6H), 2.78 (s,2H), 5.08 (s,2H).

## Example 37

## Cbz-[(ß,ß-di-Me)-ß-Ala]-Phe-$OCH_3$

A 4.0 g sample of 3-benzyloxycarbonylamino-3-methylbutanoic acid was coupled to phenylalanine methyl ester hydrochloride (3.43 g) using the mixed anhydride procedure described in Example 16. Purification of the crude product by flash chromatography eluting with 65/35 ether/hexane gave an 86% yield of product. NMR (300 MHz, $CDCl_3$): 1.32 (s,3H), 1.34 (s,3H), 2.46 (d,1H), 2.63 (d,1H), 2.98 (dd,1H), 3.09 (dd,1H), 3.70 (s,3H), 4.86 (dd,1H), 4.97 (d,1H), 5.2 (d,1H), 5.3 (s,1H), 6.13 (d,1H).

Example 38

Cbz-[(ß,ß-di-Me)-ß-Ala]-Phe-OH

To a 0°C solution of Cbz-[(ß,ß-di-Me)-ß-Ala]-Phe-OMe (1.5 g, 3.63 mmol) in dioxane (15 mL) was added a solution of lithium hydroxide (0.174 g, 4.15 mmol) in water (7.5 mL). After stirring for 1 h at 0-5°C, the reaction mixture was diluted with cold water and extracted 2X with ether. The aqueous portion was acidified with 6N HCl and extracted with ether. The organic extract was washed with brine and evaporated to give an 87% yield of product as a viscous liquid.

Example 39

Cbz-[(ß,ß-di-Me)-ß-Ala]-Phe-His Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

The product from Example 38 was coupled to the product from Example 31 using the procedure described in Example 22. There was obtained a 50% yield of the title compound.

Example 40

H-[(ß,ß-di-Me)-ß-Ala]-Phe-His Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

The resultant compound of Example 39 (0.2 g, 0.247 mmol) in acetic acid (5 mL) was hydrogenated at 1 atmosphere with 10% Pd/C (0.1 g) for 8 h. Filtration, extraction of the catalyst with acetic acid, and evaporation of the combined acetic acid solutions gave a residue which was dissolved in $H_2O$ (10 mL) and lyopholized to provide 75% of the desired product.

Example 41

3-Benzyloxycarbonylamino-2,2-dimethylpropionic Acid

3-Carbomethoxy-3-methylbutanoic acid [Bull. Soc. Chim. Fr., 828 (1965), 7.85 g, 0.049 mol] was reacted with diphenylphosphorylazide and triethylamine as described in Example 36. After heating the toluene solution for 1.5 h, benzyl alcohol (8 g) was added directly to the reaction mixture and heating at reflux

was continued for 20 h. Work-up and chromatography gave methyl 3-benzyloxycarbonyl-amino-2,2-dimethylpropionate. NMR (300 MHz, $CDCl_3$): 1.2 (s,6H), 3.3 (d,2H), 3.68 (s,3H), 5.1 (s,2H), 5.22 (m,1H). A sample of the methyl ester (6.21 g, 0.023 mol) was saponified with 3.1 g (0.78 mol) of NaOH in 100 mL ethanol/10 mL $H_2O$ at room temperature for 48 h. Work-up as in Example 36 gave the desired product as a liquid. NMR (300 MHz, $CDCl_3$): 1.23 (s,6H), 3.32 (d,2H), 5.10 (s,2H), 5.27 (m,1H).

## Example 42

## Cbz-[(α, α-di-Me)-ß-Ala]-(OMe)Tyr-$OCH_3$

To a solution of 3-benzyloxycarbonylamino-2,2-dimethylpropionic acid (1.5 g, 5.97 mmol) in methylene chloride (13 mL) was added oxalyl chloride (0.757 g, 5.97 mmol) and dimethylformamide (30 uL). After stirring for 1 h at room temperature, the reaction mixture was cooled to 0°C and treated successively with OMe-tyrosine methyl ester hydrochloride (1.465 g, 5.97 mmol) and N-methylmorpholine (1.81 g, 17.9 mmol). Stirring for 1 h at 0-5°C was followed by distribution between $CH_2Cl_2$ and 0.5 N HCl. The organic phase was washed with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was purified by chromatography. There was obtained a 61.5% yield of product as a liquid.

## Example 43

## Cbz-[(α, α-di-Me)-ß-Ala]-(OMe)Tyr-OH

To a 0°C solution of Cbz-[(α, α-di-Me)-ß-Ala]-(OMe)-Tyr-OMe (1.2 g, 2.71 mmol) in dioxane (15 mL) was added a solution of lithium hydroxide (0.115 g, 2.75 mmol) in water (7.5 mL). After stirring for 1 h at 0-5°C, the reaction mixture was diluted with cold water and extracted 2X with ether. The aqueous portion was acidified with 6N HCl and extracted with ether. The

organic extract was washed with brine and evaporated to give an 87% yield of product as a viscous liquid.

## Example 44

## H-[(α,α-di-Me)-ß-Ala]-(OMe)Tyr-His Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

Using the procedures described in Examples 39 and 40, the product from Example 43 was converted to the desired product.

## Example 45

## 2(S)-[[(4-Morpholinyl)carbonyl]oxy]-3-phenylpropionic Acid Methyl Ester

To L-phenyllactic acid methyl ester (3.2 g) was added 150 mL of 12.5% phosgene in toluene and 25 drops of dimethylformamide. After stirring for 16 h at room temperature, the solvent was evaporated and the residue chased several times with benzene. The resulting product was dissolved in methylene chloride (50 mL), cooled to 0°C and treated by dropwise addition with 3.86 g (0.044 mol) of morpholine. The reaction mixture was stirred for 2 h at 0-5°C and then distributed between 0.5 N HCl and methylene chloride. The organic phase was washed with aqueous $NaHCO_3$ and brine and evaporated to a residue. Flash chromatography on silica gel eluting with 2/1 ether-hexane gave a 65% yield of product. NMR (300 MHz): 3.08 (dd,1H), 3.20 (dd,1H), 3.8 (s,3H), 5.19 (dd,1H).

## Example 46

## 2(S)-[(4-Morpholinyl)carbonyl]oxy-3-phenylpropionic Acid

Using the hydrolysis procedure of Example 33, the title compound was obtained in 90% yield.

## Example 47

## 2(S)-[(Morpholinyl)carbonyl]oxy-3-phenylpropionyl-His Amide of(3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

Using the procedure of Example 22 with the resultant compound of Example 31 and the product from

Example 46 rather than Boc-Phe-OH, gave the desired product.

### Example 48

### 3-t-Butyloxycarbonylamino-5-methylhex-1-ene

To a stirred suspension of methyltriphenyl phosphonium bromide (10.97 g, 30.70 mmol) in anhydrous tetrahydrofuran (200 mL) at -78°C (dry ice/acetone bath) under an argon atmosphere, was added n-butyl lithium (19.8 mL of a 1.55 M hexane solution) dropwise over the course of 5 min. After 10 min, the -78°C bath was replaced with a 0°C bath for .5 h, at which time the resulting orange solution was cooled again to -78°C. The solution was then added dropwise by cannula to a stirred -78°C solution of Boc-leucinal (6.00 g, 27.91 mmol) in anhydrous tetrahydrofuran (30 mL) over the course of .5 h. The mixture was then allowed to warm to room temperature during a 3 h period after which water (150 mL) was added. Extraction with hexane (4 x 100 mL) provided a combined organic phase which was washed with brine (100 mL), dried ($Na_2SO_4$), and concentrated to give crude 3-t-butyloxycarbonylamino-5-methylhex-1-ene (6.5 g). Chromatography with ether/hexane (1/9) provided pure 3-t-butyloxycarbonylamino-5-methylhex-1-ene (3.71 g, 60%). Mass spectrum: EI, $M^+-57 = 156$; CI, $(M + H)^+ = 214$.

### Example 49

### 3-t-Butyloxycarbonylamino-5-methyl-1,2-oxohexane

To a stirred solution of 3-t-butyloxycarbonylamino-5-methylhex-1-ene (0.43 g, 2.0 mmol) in dichloromethane (20 mL) was added m-chloroperoxybenzoic acid (MCPBA, 1.51 g of 80% MCPBA, 7.0 mmol). After 68 h the reaction mixture was cooled to 0°C, and 0°C 10% $Na_2SO_3$ (5 mL) was added with stirring. After 15 min, the solid was filtered off and extracted with dichloromethane. The combined organic phase was washed sequentially with 0°C 10% $Na_2SO_3$ (6 mL), saturated $NaHCO_3$ (2 x 6 mL)

and water (5 mL). Drying ($MgSO_4$), filtering, and evaporating provided crude 3-t-butyl-oxycarbonylamino-5-methyl-1,2-oxohexane (0.42 g) which was chromatographed on 50 g of $SiO_2$ (hexane/ether, 3/1) to give pure 3-t-butyloxycarbonylamino-5-methyl-1,2-oxohexane (0.27 g, 59%). Mass spectrum: $M^+$ = 229.

Example 50

3-t-Butyloxycarbonylamino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane

To a stirred solution of 3-t-butyloxycarbonylamino-5-methyl-1,2-oxohexane (200 mg, 0.87 mmol) in methanol (8.7 mL) was added cyclohexyl mercaptan (102 mg, 0.87 mmol) and triethylamine (88 mg, 0.87 mmol). The resultant solution was refluxed for 2 h and then evaporated to give a residue which was chromatographed on 15 g of 40 u $SiO_2$ (7/3, hexane/ether) to give 281 mg (84%) of 3-t-butyloxycarbonylamino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane. Mass spectrum: $M^+$ = 345.

Anal. calcd.: C, 62.6; H, 10.2; N, 4.0.
Found: C, 62.9; H, 10.4; N, 3.9.

Example 51

3-Amino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane Hydrochloride

To a stirred solution of approximately 0.25 mmol of the resultant compound of Example 50 in methanol was added methanolic HCl (10 mL of approximately 0.75 M HCl). After 8 to 12 h, the solvent was evaporated, and the desired compound was used without further purification.

Example 52

Boc-His Amide of 3-Amino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane

To a stirred suspension of Boc-His-OH (72 mg, 0.28 mmol) in dry dimethylformamide (3 mL) at -23°C was added a solution of 3-amino-1-cyclohexylmercapto-

2-hydroxy-5-methylhexane hydrochloride (derived from 98 mg, 0.28 mmol, of 3-t-butyl-oxycarbonylamino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane using the procedure of Example 51) in dry dimethylformamide (2 mL) containing N-methylmorpholine (29 mg, 0.28 mmol). Hydroxybenzotriazole (HOBT, 58 mg, 0.43 mmol) and N,N'-dicyclohexylcarbodiimide (DCC, 59 mg, 0.28 mmol) were then added sequentially. After 2 h the mixture was allowed to warm to room temperature. After 22 h the mixture was filtered, evaporated, and partitioned between ethyl acetate (18 mL) and saturated aqueous $NaHCO_3$ (6 mL). The layers were separated, and the organic phase was washed with brine (5 mL), dried ($Na_2SO_4$), filtered, and evaporated to a solid which was chromatographed on $SiO_2$ (9/1, dichloromethane/methanol) to give 86 mg (63%) of the desired compound. Mass spectrum: $(M+H)^+ = 483$.

## Example 53

## Boc-Phe-His Amide of 3-Amino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane

The resultant compound of Example 52 was treated with methanolic HCl according to the procedure used in Example 51, yielding the corresponding deprotected HCl salt which was used as described below without further purification. To a stirred -12°C solution of Boc-Phe-OH (19.2 mg, 0.0725 mmol) in anhydrous tetrahydrofuran (3 mL) was added N-methylmorpholine (8.0 1, 0.0725 mmol) in a dropwise fashion followed by isobutylchloroformate (9.4 1, 0.0725 mmol). After 3 min, a -12°C solution of the above HCl salt in anhydrous tetrahydrofuran (2 mL) containing N-methylmorpholine (16.0 1, 0.145 mmol) was added over the course of 30 sec. After 15 min, the mixture was allowed to warm to room temperature for 3 h at which time the solvent was evaporated, and the residue was partitioned between ethyl acetate (20 mL) and saturated $NaHCO_3$

(6 mL). The layers were separated and the organic phase was washed with brine (5 mL). Drying ($Na_2SO_4$), evaporating, and chromatographing the resulting solid on $SiO_2$ (9/1, dichloromethane/methanol) provided 11 mg of the desired compound (24% yield). Mass spectrum: $(M+H)^+ = 630$.

### Example 54

### (4R)-3-(3-Phenylpropionyl)-4-(2-propyl)-oxazolidine-2-one

To a stirred solution of 4-(2-propyl)-oxazolidine-2-one in anhydrous tetrahydrofuran (250 mL) under a nitrogen atmosphere at -78°C were added in a dropwise fashion a solution of n-butyllithium in hexane (50 mL, 77.4 mmol) over 5 to 10 min. After stirring an additional 20 min at -78°C 3-phenylpropionyl chloride (12.7 mL, 85.2 mmol) was added neat. The reaction was warmed to room temperature and stirred 1 to 2 h at the temperature. The reaction was quenched by adding 100 mL of saturated aqueous ammonium chloride and the volatiles removed by rotary evaporation. The resulting aqueous residue was extracted three times with ether and the combined organic phases were washed with brine, dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Recrystallization from hexanes/ethyl acetate provided the title compound (16.6 g, 82%). mp = 86.5 to 87.5°C. Mass spectrum: $(M+NH_4)^+ = 279$, $(M+H)^+ = 262$.

### Example 55

### (4R)-3-[(2-R)-2-(t-butyl acetyl)-3-phenylpropionyl]-4-(2-propyl)-oxazolidine-2-one

To a stirred solution of the product resulting from Example 54 (2.28 g, 8.72 mmol), in anhydrous tetrahydrofuran (30 mL) under a nitrogen atmosphere at -78°C was added a solution of sodium hexamethyldisilylamide (9.6 mL, 9.59 mmol) in tetrahydrofuran. After stirring for 30 min at -78°C, t-butyl bromoacetate (2.21 g, 11.34 mmol) was added in anhydrous tetrahydrofuran and the

resulting solution stirred 1 h at -78°C. The reaction was quenched by adding 20 mL of saturated aqueous ammonium chloride and partitioned between water and ether. The aqueous layer was drawn off and extracted with ether. The combined organic phases were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($Na_2SO_4$), filtered, and concentrated in vacuo. Recrystallization from acetone/hexanes provided the desired purified product (2.59 g, 79%). m.p. = 167-168°C. Mass spectrum: $(M+NH_4)^+ = 393$, $(M+H)^+ = 376$.

Example 56

Benzyl (2R)-2-(t-butyl acetyl)-3-phenyl-propionate

To a stirred solution of dry benzyl alcohol (0.55 mL, 5.33 mmol) in anhydrous tetrahydron furan (18 mL) under a nitrogen atomosphere at 0°C was added a hexane solution of n-butyllithium (2.58 mL; 4.00 mmol). To this solution was added the product from Example 55 in anhydrous tetrahydrofuran (10 mL). After stirring 1 h at 0°C the reaction was quenched by adding excess saturated aqueous ammonium chloride. The volatiles were removed by rotary evaporation and the resulting aqueous residue extracted two times with ether. The combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered, and concentrated in vacuo provided an oil which was purified by chromatography on $SiO_2$ (15% ethyl acetate/hexanes) to provide the desired product (0.89 g, 94%) as a colorless oil. Mass spectrum: $(M)^+ = 354$.

Example 57

Benzyl (2R)-2-acetyl-3-phenylpropionate

The product from Example 56 (0.52 g, 1.47 mmol) was dissolved in a 1:1 (v:v) solution (6 mL) of trifluoroacetic acid and dichloromethane and stirred at room temperature for 1 h. The volatiles were removed in vacuo to provide the title compound (0.437 g, 100%) as

an oil which crystallized on standing. The unpurified material was of sufficient purity to employ in subsequent steps. Mass spectrum: $(M)^+ = 298$.

Example 58

Benzyl-(2R)-2-benzyl-3-(N-morpholinocarbamoyl)propionate

The product from Example 57 (0.438 g, 1.47 mmol), diphenylphosphoryl azide (317 uL, 1.47 mmol), and triethylamine (205 uL, 1.47 mmol) in dry benzene (6 mL) were refluxed for 3 to 5 h to provide a solution of the derived isocyanate which was cooled to 0°C and treated with morpholine (141 uL, 1.62 mL). The cooling bath was removed and the reaction stirred for 1 h. The reaction mixture was poured into 10% aqueous HCl and extracted two times with ether. The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo to provide the unpurified product. The desired product (0.403 g, 72%) was obtained in pure form after chromatography on $SiO_2$ (3% methanol/chloroform) as a thick oil which formed an amorphous solid on standing. Mass spectrum: $(M)^+ = 382$. NMR (300 MHz, $COCl_3$, ppm, TMS as internal standard) 7.12-7.40 (m, 10H), 5.18 (AB; J=12.6 Hz; 2H), 4.8 (dd; J=5.7 Hz; 1H), 3.59 (d,d; J=6.0, 6.0 Hz; 4H), 3.55 (d,d,d; J=3.0, 6.0, 14.4 Hz; 1H), 3.37 (d,d,d; J=5.4, 8.4, 14.4 Hz; 1H), 3.13 (d,d; J=6.0, 6.0 Hz; 4H), 2.8-3.10 (m, 3H).

Example 59

Benzyl (2R)-2-benzyl-3-(ethoxycarbamoyl)propionate

The procedure as described in Example 58 was followed except absolute ethanol was employed in lieu of morpholine. Mass spectrum: $(M)^+ = 341$. NMR (300 MHz, $CDCl_3$, ppm, TMS as internal standard) 7.1- 7.4 (m,10H), 5.17 (s,2H), 4.96 (br s,1H), 4.07 (d,d,d; J=6.6, 6.6, 6.6 Hz,2H), 3.25-3.5 (2 br ABX,2H), 2.9-3.05 (m,2H), 2.75-2.88 (br m,1H), 1.23 (d,d; J=6.6, 6.6 Hz;

3H).

Example 60

(2R)-2-Benzyl-3-(morpholinocarbamoyl)propionate

The product from Example 58 (0.315 g, 0.86 mmol) was dissolved in ethyl acetate (5 mL) and syringed into a flask charged with 10% Pd/C (¨0.3 g). The resulting suspension was exposed to 1 atm of gaseous hydrogen for 2 to 4 h. The catalyst was removed by filtration through a celite pad. The filtrate was concentrated in vacuo to provide the desired compound (0.21 g, 88%) as a cream colored foam which was employed without further purification. Mass spectrum: $(M+H)^+$ = 278.

Example 61

(2R)-2-Benzyl-3-ethoxycarbamoylpropionate

The procedure as described in Example 60 was followed employing the product from Example 59 in lieu of that from Example 58. Mass spectrum: $(M+H)^+$ = 252.

Example 62

Benzyl (2R)-2-benzyl-3-morpholinocarbonylpropionate

The product of Example 57 was converted to the title compound using the mixed anhydride method of coupling as described in Example 53. Mass spectrum: $(M)^+$ = 367.

Example 63

(2R)-2-Benzyl-3-morpholinocarbonylpropionate

The product from Example 62 was converted to the title compound following the procedure described in Example 60. Mass spectrum: $(M)^+$ = 277.

Example 64

(2R)-2-Benzyl-3-(morpholinocarbamoyl)-propionyl-His Amide of 3-Amino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane

The resultant compound from Example 52 was treated with ethanolic HCl according to the procedure in Example 51, yielding the corresponding HCl salt which

was used as described below without further purification. Coupling of the resultant compound from Example 60 with the above salt was performed, in analogy to the procedure of Example 52, to provide the desired compound.

Example 65

(2R)-2-Benzyl-3-(morpholinocarbonyl)-propionyl-His Amide of 3-Amino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane

Using the procedure from Example 64 with the resultant compound from Example 63 provided the desired compound.

Example 66

2-t-Butyloxycarbonylamino-1-cyclohexylbut-3-ene

Using the procedure of Example 48 but replacing Boc-leucinal with Boc-cyclohexylalaninal, gave the desired compound. Mass spectrum: $(M+H)^+ = 254$.

Example 67

3-t-Butyloxycarbonylamino-4-cyclohexyl-1,2-oxobutane

Using the procedure of Example 49 with the resultant compound of Example 66 gave the desired compound. Mass spectrum: $(M+H)^+ = 270$.

Example 68

3-t-Butyloxycarbonylamino-4-cyclohexyl-2-hydroxy-1-isopropylmercaptobutane

Using the procedure of Example 50 with the resultant cmpound of Example 67, but replacing cyclohexl mercaptan with isopropyl mercaptan, gave the desired compound. Mass spectrum: $(M+H)^+ = 346$.

Example 69

3-t-Butyloxycarbonylamino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

Treating the resultant compound of Example 68 with 2.5 equivalents of 3-chloroperoxy-benzoic acid in dichloromethane, gave the desired compound after work-up as described in Example 49. Mass spectrum: $(M+H)^+ = 418$.

Anal. , calcd. for $C_{21}H_{33}NO_5S \cdot 0.5\ H_2O$: C, 59.10; H, 9.45; N, 3.28.

Found: C, 58.90; H, 9.46; N, 3.03.

Example 70

Boc-His Amide of 3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

The resultant compound of Example 69 was deprotected in analogy to Example 51 and coupled to Boc-His OH according to Example 52 to provide the desired compound. Mass spectrum: $(M)^+ = 514$.

Example 71

Boc-Leu Amide of 3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

The resultant compund of Example 69 was deprotected in analogy to Example 51 and coupled to BocLeuOH in analogy to Example 53 to provide the desired compound. Mass spectrum: $(M+H)^+ = 491$.

Example 72

(2R)-2-Benzyl-3-(morpholinocarbonyl)-propionyl-His Amide of3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

Using the procedure of Example 65 with the resultant compound of Example 70 provided the desired compound. Mass spectrum: $(M+H)^+ = 674$.

Example 73

(2R)-2-Benzyl-3-(morpholinocarbonyl)-propionyl-Leu Amide of3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

Using the procedure of Example 65 with the resultant compound of Example 71 provided the desired compound.

Example 74

(2S)-2-Benzyl-3-(ethoxycarbamoyl)-propionyl-His Amide of 3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

Using the procedure of Example 64 with the resultant compounds of Examples 61 and 70 provided the

desired compound., Mass spectrum: $(M+H)^+ = 648$.

Anal. calcd. for $C_{32}H_{49}N_5O_7S \cdot 1.5H_2O$: C, 56.95; H, 7.77; N, 10.38.

Found: C, 56.99; H, 7.47; N, 10.27.

Example 75

(2S)-2-Benzyl-3-(ethoxycarbamoyl)-propionyl-Leu Amide of 3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

Using the procedure of Example 74 with the resultant compound of Example 71 in lieu of the resultant compound from Example 70, provided the desired compound.

Example 76

(3S,4S)-3-hydroxy-4-t-butyloxycarbonyl-amino-5-cyclohexylpentanenitrile

To a solution of lithium diisopropylamide (4.40 mmol) in dry tetrahydrofuran (4 mL) at -78°C was added acetonitrile (0.25 mL, 4.4 mmol). To this enolate suspension was added 2(S)-t-butyloxycarbonylamino-3-cyclohexylpropanal (0.76 g, 2.98 mmol) in tetrahydrofuran (5 mL) pre-cooled to -78°C. After stirring for 15 min, the mixture was quenched with 2M HCl (2.3 mL), warmed to -10°C, acidified with 2M HCl (5.0 mL), and extracted with ether which was dried over $MgSO_4$ and evaporated. Flash chromatography on silica gel with ethyl acetate/hexane mixtures afforded 0.360 g (41%) of the desired compound as an oil.

Anal. Calcd for $C_{16}H_{28}N_2O_3 \cdot 0.4\ H_2O$: C, 63.30; H, 9.56; N, 9.23.

Found: C, 63.51; H, 9.66; N, 8.81.

Example 77

(3S,4S)-1-Amino-3-hydroxy-4-t-butyloxycarbonylamino-5-cyclohexylpentane

(3S,4S)-3-Hydroxy-4-t-butyloxycarbonylamino-5-cyclohexylpentane nitrile (0.2300 g, 0.766 mmol) and Raney nickel (0.230 g) were hydrogenated at 3 atm in methanol (20 mL) and ammonia (15 mL). The mixture was

filtered, evaporated, dissolved in ethyl acetate and extracted with 0.5 M $H_3PO_4$. The aqueous phase was made basic with solid $K_2CO_3$ and extracted with 25% isopropanol in chloroform which was dried over $Na_2SO_4$ and evaporated to afford 0.1520 g (65%) of the desired product as an oil. Exact mass calculated for $C_{16}H_{32}N_2O_3$: 300.2411. Found: 300.2439.

Example 78

(3S,4S)-1-(3-Methylbutylcarbonylamino)-3-hydroxy-4-t-butyloxycarbonylamino-5-cyclohexylpentane

To (3S,4S)-1-amino-3-hydroxy-4-t-butyloxycarbonylamino-5-cyclohexylpentane (30.8 mg, 0.102 mmol) in dry methylene chloride (3 mL) at 0°C was added 4-methylpentanoyl chloride (17.0 uL, 0.123 mmol) and triethylamine (20.0 uL, 0.143 mmol). The mixture was stirred at 0°C for 1 h, evaporated, taken up in methanol (3 mL) and treated with 1 M NaOH (1 mL). After stirring for 1 h, the mixture diluted with ether, washed sequentially with 0.5 M $H_3PO_4$, saturated $NaHCO_3$ solution, and brine, and then dried over $Na_2SO_4$ and evaporated to afford 41.0 mg (100%) of the desired product as an oil.

Analysis Calculated for $C_{16}H_{28}N_2O_3$· 0.25 $H_2O$: C, 65.55; H, 10.63; N, 6.95.

Found: C, 65.52; H, 11.02; N, 6.77.

Example 79

Boc-Phe-His Amide of (3S,4S)-1-(3-Methylbutylcarbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

The resultant compound from Example 78 (36.9 mg, 0.0926 mmol) was stirred for 1 h in 4 M HCl in dioxane. The solvent was removed and dimethylformamide (0.5 mL) and N-methylmorpholine (23 uL, 0.21 mmol) were added.

To Boc-Phe-His-OH (38.5 mg, 0.0957 mmol) and 1-hydroxybenzotriazole (39.5 mg, 0.292 mmol) in dimethylformamide (0.3 mL) at -23°C was added 1-ethyl-

3-dimethylaminopropylcarbodiimide hydrochloride (18.9 mg, 0.0986 mmol). After 1 h the amine solution was added and after an additional 2 h, the mixture was warmed to room temperature and stirred for 18 h. The mixture was poured into saturated $NaHCO_3$ solution and extracted into ethyl acetate which was washed with water and brine, then dried over $Na_2SO_4$ and evaporated. Chromatography of the residue on silica gel with 3% $CH_3OH/CHCl_3$ afforded 43.3 mg (69%) of a white solid, m.p. 168-172°C.

Example 80

Boc-His Amide of (3S,4S)-1-(3-Methylbutylcarbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

Using the procedure of Example 79 with the resultant compound of Example 78 and Boc-His-OH rather than Boc-Phe-His-OH, gave the desired compound.

Example 81

(3S,4S)-1-(2-Propylsulfonylamino)-3-hydroxy-4-t-butyloxycarbonylamino-5-cyclohexylpentane

Using the procedure of Example 78 employing the resultant compound from Example 77 and isopropylsulfonyl chloride instead of 4-methylpentanoyl chloride afforded the desired compound.

Example 82

Boc-Phe-His Amide of (3S,4S)-1-(2-Propylsulfonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

Using the procedure of Example 79 employing the resultant compound from Example 81 gave the desired compound, m.p. 174-177°C.

Example 83

Boc-Phe-dl-3-pyrazolylalanine Methyl Ester

To dl-3-pyrazolylalanine methyl ester dihydrochloride (dl connotes 50/50 mixture of dextrorotatory/levorotatory) (2.05 g, 8.5 mmol) in dimethylformamide (10 mL) at -10°C was added Boc-Phe N-hydroxysuccinimide

ester (2.50 g, 6.90 mmol) and N-methylmorpholine (2.8 mL, 25 mmol). The mixture was stirred at -10°C for 1 h and then at 25°C for 12 h. The mixture was partitioned between ethyl acetate and saturated $NaHCO_3$ solution, and extracted with ethyl acetate which was washed with water, dried over $Na_2SO_4$ and evaporated to afford 2.75 g (95%) of the desired product.

Analysis calculated for $C_{21}H_{28}N_4O_5 \cdot 0.25\ H_2O$: C, 59.92; H, 6.82; N, 13.31.

Found: C, 59.82; H, 6.75; N, 13.13.

Example 84

Boc-Phe-dl-3-pyrazolylalanine

Boc-Phe-dl-3-pyrazolylalanine methyl ester (0.210 g, 0.505 mmol) in dioxane (1.5 mL) and water (1.0 mL) was treated with lithium hydroxide monohydrate (0.0272 g, 0.648 mmol), stirred at 25°C for 30 min and quenched with 0.32 mL 2 M HCl. The mixture was poured into chloroform, washed with water, dried over $Na_2SO_4$ and evaporated to afford 0.184 g (91%) of the desired compound.

Analysis calculated for $C_{20}H_{26}N_4O_5 \cdot 0.25\ H_2O$: C, 59.03; H, 6.56; N, 13.77.

Found: C, 58.66; H, 6.70; N, 13.65.

Example 85

Boc-Phe-dl-3-pyrazolylalanine Amide of (3S,4S)-1-(3-Methylbutylcarbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

Using the procedure of Example 79 with the resultant compound from Example 78 and using the resultant compound from Example 84 rather than Boc-Phe-His-OH afforded the desired compound.

Anal. Calcd for $C_{37}H_{58}N_6O_6 \cdot 0.75\ H_2O$: C, 63.81; H, 8.61; N, 12.07.

Found: C, 63.95; H, 8.70; N, 11.79.

## Example 86

## Ethyl (3R,4S)-3-hydroxy-4-t-butyloxycarbonylamino-2,2-difluoro-5-cyclohexylpentanoate

Boc-cyclohexylalanal (6.60 g, 25.8 mmol) in dry tetrahydrofuran (THF, 100 mL) was treated with ethyl bromodifluoroacetate (10.5 g, 51.7 mmol) and zinc dust (4.25 g, 65.0 mmol). The mixture was subjected to ultrasonic mixing (15-25°C) for 2 h, then poured into saturated aqueous $NaHCO_3$ solution which was extracted with ethyl acetate. The organic phases were dried over $Na_2SO_4$, evaporated, and the residue was chromatographed on silica gel with ethyl acetate/hexane mixtures to afford 3.27 g (33%) of the desired compound and 1.45 g (15%) of the 3S isomer. 3R isomer: m.p. 106-109°C; 3S isomer: m.p. 71-73°C.

## Example 87

## (3R,4S)-1,3-dihydroxy-2,2-difluoro-4-t-butyloxycarbonylamino-5-cyclohexylpentane

To the resultant compound from Example 86 (525.0 mg, 1.38 mmol) in methanol (6 mL) was added $NaBH_4$ (106 mg, 2.8 mmol). The mixture was stirred for 1 h, poured into saturated aqueous $NaHCO_3$ solution, and extracted with ethyl acetate which was dried over $Na_2SO_4$ and evaporated to afford 467 mg (100%) of the desired product. DCI-MS: $(M+H)^+ = 338$.

## Example 88

## (3R,4S)-4-Cyclohexylmethyl-5-(2-hydroxy-1,1-difluoroethyl)-2-oxazolidinone

The resultant compound from Example 87 (596 mg, 1.77 mmol) in dry dimethylformamide (DMF, 15 mL) was added to NaH (260 mg, 6.5 mmol, 60% in oil, hexane washed) in DMF (5 mL) at 0°C. The mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution and the organic phase was dried over $Na_2SO_4$

and evaporated to afford 472 mg (100%) of product as an oil.

Anal. Calcd for $C_{12}H_{19}F_2NO_3$·0.25 $H_2O$: C, 53.82; H, 7.34; N, 5.23.

Found: C, 54.01; H, 7.05; N, 5.32.

Example 89

(3R,4S)-4-Cyclohexylmethyl-5-(2-mesyloxy-1,1-difluoroethyl)-2-oxazolidinone

To the resultant compound from Example 88 (460 mg, 1.75 mmol) in $CH_2Cl_2$ (5 mL) at 0°C was added triethylamine (0.36 mL, 2.6 mmol) and methanesulfonyl chloride (135 uL, 1.74 mmol). After stirring at 0°C for 20 min, the mixture was diluted with ethyl acetate, washed sequentially with 0.5 M $H_3PO_4$, saturated aqueous $NaHCO_3$ solution, and brine, then dried over $Na_2SO_4$ and evaporated to afford 558 mg (94%) product as an oil. Mass spectrum: FAB, $(M+H)^+ = 342$.

Example 90

(3R,4S)-4-Cyclohexylmethyl-5-(2-azido-1,1-difluoroethyl)-2-oxazolidinone

To the resultant compound from Example 89 (179.9 mg, 0.527 mmol) in dimethylformamide (DMF, 3 mL) was added $NaN_3$ (111.0 mg, 1.71 mmol) and the mixture was heated 100-110°C for 16 h. The mixture was poured into ethyl acetate which was washed with water and brine, dried over $Na_2SO_4$ and evaporated. Chromatography of the residue on silica gel with ethyl acetate/hexane mixtures afforded 116.9 mg (77%) product as an oil. Mass specrum: EI, $(M+H)^+ = 289$.

Example 91

(3R,4S)-4-Cyclohexylmethyl-5-(2-isopropylmercapto-1,1-difluoroethyl)-2-oxazolidinone

To NaH (85.0 mg, 2.22 mmol, 60% in oil, hexane washed) in DMF (4 mL) at 0°C was added isopropylmercaptan (0.40 mL, 4.3 mmol). After 15 min the

resultant compound from Example 89 (373.4 mg, 1.09 mmol) in DMF (4 mL) was added and the mixture was heated 50-60°C for 16 h. The mixture was poured into ethyl acetate which was washed with water and brine, dried over $Na_2SO_4$ and evaporated. Chromatography of the residue on silica gel with ethyl acetate/hexane mixtures afforded 258.0 mg (73%) product as a solid, m.p. 75-76°C.

Anal. Calcd for $C_{15}H_{25}F_2NO_2S$: C, 56.05; H, 7.84; N, 4.36.

Found: C, 56.09; H, 8.02; N, 4.14.

Example 92

(3R,4S)-4-Cyclohexylmethyl-
5-(2-isopropyloxy-1,1-difluoroethyl)-2-oxazolidinone

Using the procedure of Example 91 and isopropanol instead of isopropyl mercaptan afforded the desired product.

Example 93

(3R,4S)-3-Hydroxy-4-amino-2,2-difluoro-
1-azido-5-cyclohexylpentane

To the resultant compound from Example 90 (113.9 mg, 0.395 mmol) in dioxane (4.5 mL) and water (3 mL) was added $Ba(OH)_2 \cdot 8\ H_2O$ (0.25 g, 0.79 mmol) and the mixture was heated at reflux for 13 h. The mixture was filtered, and the filtrate was concentrated, partitioned between water and ether, and extracted with ether. The organic extract was dried over $Na_2SO_4$ and evaporated to afford 108 mg (100%) product as an oil. Mass spectrum: FAB, $(M+H)^+ = 263$.

Example 94

(3R,4S)-3-Hydroxy-4-amino-2,2-difluoro-1-isopropyloxy-
5-cyclohexylpentane

Using the procedure of Example 93 with the resultant compound from Example 92 afforded the desired compound.

Example 95

Boc-Phe-Leu Amide of (3R,4S)-3-hydroxy-4-amino-2,2-difluoro-1-azido-5-cyclohexylpentane

To Boc-Phe-Leu-OH (169.8 mg, 0.449 mmol) in THF (2 mL) at -10°C was added N-methylmorpholine (48 uL, 0.44 mmol) followed by isobutyl chloroformate (57 uL, 0.44 mmol). After 3 min, the resultant compound from Example 93 (105.0 mg, 0.40 mmol) in THF (4 mL) was added and the reaction was stirred at -10°C 15 min then at room temperature for 2 h. The mixture was diluted with ethyl acetate, washed sequentially with 0.5 M $H_3PO_4$, saturated aqueous $NaHCO_3$ solution, and brine, then dried over $Na_2SO_4$ and evaporated. Chromatography of the residue on silica gel with ethyl acetate/hexane mixtures afforded 184.0 mg (74%) product as a glass. NMR (300 MHz, $CDCl_3$, ppm): 0.9 (d,6H), 1.4 (S,9H), 3.15-3.00 (m,2H), 3.80-3.60 (m,3H), 4.05-3.95 (m,1H), 4.4-4.2 (m,2H), 4.85 (d,1H), 5.10 (d,1H), 6.15 (d,1H).

Example 96

Boc-Phe-Leu Amide of (3R,4S)-3-hydroxy-4-amino-2,2-difluoro-1-isopropyloxy-5-cyclohexylpentane

Using the procedure of Example 95 with the resultant compound from Example 94 afforded the desired product.

Example 97

Boc-Phe-Leu Amide of (3R,4S)-3-hydroxy-4-amino-2,2-difluoro-1-isopropylmercapto-5-cyclohexylpentane

Using the procedure of Example 95 and the resultant compound from Example 91 which had been hydrolyzed to the free amine according to the procedure in Example 93 afforded the desired product.

Anal. Calcd for $C_{34}H_{55}F_2N_3O_5S$: C, 62.26; H, 8.45; N, 6.41.

Found: C, 62.32; H, 8.78; N, 6.19.

Example 98

Boc-Phe-Leu Amide (4-amino) of (3R,4S)-3-hydroxy-1,4-diamino-2,2-difluoro-5-cyclohexylpentane

The resultant compound from Example 95 (72.0 mg) and 10% palladium on carbon (42 mg) in methanol (3 mL) and acetic acid (1 mL) were stirred under a hydrogen atmosphere for 8 h. The mixture was filtered, concentrated, and partitioned between ethyl acetate and 1 M aqueous $Na_2CO_3$ solution. The organic extracts were dried over $Na_2SO_4$ and evaporated to afford 63.2 mg (92%) of the desired product as a solid. Mass spectrum: EI, $M^+ = 596$.

Example 99

Boc-Phe-Leu Amide of (3R,4S)-3-hydroxy-4-amino-2,2-difluoro-1-isopentylcarbonylamino-5-cyclohexylpentane

To the resultant compound from Example 98 (586 mg, 0.0982 mmol) in $CH_2Cl_2$ (2 mL) at 0°C was added N-methylmorpholine (16 uL, 1.5 mmol) and iso-caproyl chloride (15 uL, 0.11 mmol). After stirring at room temperature for 1 h the mixture was diluted with ethyl acetate, washed sequentially with 0.5 M $H_3PO_4$, saturated aqueous $NaHCO_3$ solution and brine, dried over $Na_2SO_4$ and evaporated. Chromatography of the residue on silica gel with ethyl acetate/hexane mixtures afforded 39.6 mg (58%) product as a solid.

Anal. Calcd for $C_{37}H_{60}F_2N_4O_6$: C, 63.95; H, 8.70; N, 8.06.

Found: C, 64.07; H, 9.07; N, 7.73.

Example 100

Boc-Phe-Leu Amide of (3R,4S)-3-hydroxy-4-amino-2,2-difluoro-1-isopropylsulfonyl-5-cyclohexylpentane

To the resultant compound from Example 97 (50.0 mg, 0.0762 mmol) in $CH_2Cl_2$ (2 mL) was added m-chloroperbenzoic acid (42.0 mg, 0.20 mmol, 80% pure). After 1 h the mixture was diluted with ethyl acetate,

washed sequentially with cold 10% aqueous $Na_2SO_3$ solution, saturated aqueous $NaHCO_3$ solution and brine, then dried over $Na_2SO_4$ and evaporated. Chromatography on silica gel with ethyl acetate/ hexane mixtures provided 42.4 mg (81%) product as a solid.

Anal. Calcd for $C_{34}H_{55}F_2N_3O_7S$: C, 59.37; H, 8.06; N, 6.11.

Found: C, 59.05; H, 8.33; H, 5.76.

Example 101

Boc-Phe-Leu Amide of (4S)-3-oxo-4-amino-2,2-difluoro-1-azido-5-cyclohexylpentane

To oxalyl chloride (19 uL, 0.22 mmol) in $CH_2Cl_2$ (1 mL) at -60°C was added dimethylsulfoxide (24 uL, 0.34 mmol) in $CH_2Cl_2$ (1 mL). After 15 min the resultant compound from Example 95 (44.0 mg, 0.0707 mmol) in $CH_2Cl_2$ (3 mL) was added. The reaction was stirred for 20 min and triethylamine (75 uL, 0.54 mmol) was added. The mixture was stirred for 20 min, poured quickly into cold 20% saturated aqueous $NaHSO_4$ solution and diluted with ethyl acetate (4 mL) and hexane (12 mL). The organic phase was washed with water then brine, dried over $Na_2SO_4$ and evaporated. Chromatography of the residue on silica gel with ethyl acetate/hexane mixtures provided 37.3 mg (85%) product as a solid. Mass spectrum: EI, $M^+ = 620$.

Example 102

Boc-Phe-Leu Amide of (4S)-3-oxo-4-amino-2,2-difluoro-1-isopropylsulfonyl-5-cyclohexylpentane

Using the procedure of Example 101 with the resultant compound from Example 100 afforded the desired product as a solid.

Anal. Calcd for $C_{34}H_{53}F_2N_3O_7S \cdot 0.5\ H_2O$: C, 58.77; H, 7.83; N, 6.05.

Found: C, 58.85; H, 7.87; N, 5.90.

Example 103

Boc-Phe-Leu Amide of (4S)-3-oxo-4-amino-2,2-difluoro-1-isopropyloxy-5-cyclohexylpentane

Using the procedure of Example 101 with the resultant compound from Example 96 provided the desired product.

Example 104

Boc-Phe-Leu Amide of (4S)-3-oxo-4-amino-2,2-difluoro-1-isopropylmercapto-5-cyclohexylpentane

Using the procedure of Example 101 with the resultant compound from Example 97 provided the desired product as a solid.

Anal. Calcd for $C_{34}H_{53}F_2N_3O_5S \cdot 0.5 H_2O$: C, 61.61; H, 8.21; N, 6.34.

Found: C, 61.68; H, 8.25; N, 6.22.

Example 105

Boc-Phe-Leu Amide of (4S)-3-oxo-4-amino-2,2-difluoro-1-isopentylcarbonylamino-5-cyclohexylpentane

Using the procedure of Example 101 with the resultant compound from Example 99 provided the desired product as a solid.

Anal. Calcd for $C_{37}H_{58}F_2N_4O_6$: C, 64.14; H, 8.44; N, 8.09.

Found: C, 63.84; H, 8.43; N, 7.89.

Example 106

(2S,3S)-1-Azido-3-t-butyloxycarbonylamino-2-hydroxy-5-methylhexane

A stirred solution of the resultant compound of Example 49 (1.0 mmol) in methanol (10 mL) was refluxed with sodium azide (2.4 mmol) and ammonium chloride (1.8 mmol) for 2 h. The solvent was evaporated, and the residue was extracted with several portions of hot chloroform. The extract was filtered and evaporated to a residue which was chromatographed on $SiO_2$ eluting with hexane/ether mixtures to give the desired compound in 76% yield, m.p. = 50-52°C.

Example 107

(2S,3S)-1-Amino-3-t-butyloxycarbonylamino-2-hydroxy-5-methylhexane Hydrochloride

The resultant compound of Example 106 (400 mg) dissolved in methanol containing added $CHCl_3$ was hydrogenated over 10% Pd/C (40 mg) with 3 atmospheres hydrogen. Filtration and evaporation gave the desired compound (305 mg).

Example 108

(2S,3S)-3-t-Butyloxycarbonylamino-2-hydroxy-1-(isovalerylamino)-5-methylhexane

To a solution of the resultant compound of Example 107 (1.0 mmol) and triethyl amine (2.0 mmol) in chloroform (10 mL) cooled to 0°C was added isovaleryl chloride (1.0 mmol) in $CHCl_3$ (2 mL). After 3 h, the solution was washed sequentially with 10% citric acid, saturated $NaHCO_3$, and brine. Drying and evaporating provided the desired compound.

Example 109

(2S,3S)-1-Azido-2-hydroxy-3-t-butyloxycarbonylamino-4-cyclohexylbutane

The resultant compound from Example 67 was treated according to the procedure of Example 106 to give the desired compound.

Anal. Calcd for $C_{15}H_{28}N_4O_3$: C, 57.67; H, 9.03; N, 17.93.

Found: C, 57.54; H, 9.14; N, 17.57.

Example 110

Boc-Phe-His Amide of (2S,3S)-1-(Isovalerylamino)-2-hydroxy-3-amino-5-methylhexane

Using the procedure of Example 79 with the resultant compound from Example 108 gave the desired compound.

Anal. Calcd for $C_{32}H_{50}N_6O_6 \cdot 0.5\ H_2O$: C, 61.62; H, 8.24; H, 13.47.

Found: C, 61.68; H, 8.31; N, 13.34.

Example 111

Boc-Phe-His Amide of (2S,3S)-1-Azido-2-hydroxy-3-amino-4-cyclohexylbutane

Using the procedure of Example 79 with the resultant compound from Example 109 gave the desired compound.

Anal. Calcd for $C_{30}H_{44}N_8O_5 \cdot H_2O$; C, 58.62; H, 7.54; N, 18.22.

Found: C, 58.71; H, 7.45; N, 18.22.

Example 112

4(S)-t-Butyloxycarbonylamino-5-cyclohexyl-3(R,S)-hydroxyl-1-pentene.

To a stirred -78°C solution of Boc-cyclohexylalanine methyl ester (10.2 g, 35.8 mmol) in dry toluene (60 mL) was added diisobutylaluminum hydride (34 mL of a 1.5 M solution in toluene). After 30 min, vinyl magnesium bromide (108 mL of 1 M solution in tetrahydrofuran (THF)) was added. After stirring for 15 h at 0°C, the mixture was carefully quenched with methanol, treated with Rochelle salts (22 mL of saturated aqueous solution in 140 mL $H_2O$), and filtered. After extracting the solids 5 times with ethyl acetate, the extracts and filtrate were combined and the organic phase was washed with brine, dried, filtered and evaporated to an oil (10.2 g). Chromatography on silica gel eluting with hexane/ethyl acetate mixtures provided 6.1 g (60%) of the desired product.

Anal. Calcd for $C_{16}H_{29}NO_3 \cdot H_2O$: C, 66.8; H, 10.3; H, 4.9.

Found: C, 66.9; H, 10.2; N, 4.7.

Example 113

4(S)-Cyclohexylmethyl-5(R,S)-vinyl-2-oxazolidinone

The resultant product of Example 112 (2.80 g, 9.88 mmol) in dry dimethylformamide (DMF) (50 mL) was added to a stirred suspension of NaH (593 mg of a 60% dispersion in oil, 14.8 mmol, hexane washed) in dry DMF

(50 mL). After 3 h, the mixture was quenched (750 mL water + 100 mL brine) and extracted with ether (5 x 100 mL). The combined organic phase was washed with brine (3 x 50 mL), dried ($MgSO_4$), filtered and evaporated to an oil (2.23 g). The NMR spectrum of the crude product revealed an 82:18 mixture of 5S:5R diastereomers. Silica gel chromatography gave 80% recovery of pure diastereomers.

5S: Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.9; H, 9.1; N, 6.7. Found: C, 68.4; H, 9.2; N, 6.5. Mass spectrum: $(M+1)^+ = 210$.

5R: Mass spectrum: $(M+1)^+ = 210$.

Example 114

(3S,4S)-3-Hydroxy-4-amino-5-cyclohexyl-1-pentene

To the resultant 5S-diasteriomer from Example 113 (2.06 g, 9.84 mmol) in dioxane (180 mL) and water (120 mL) was added barium hydroxide octahydrate (6.24 g, 19.8 mmol). The mixture was refluxed for 18 h, cooled, filtered, concentrated, taken up in water and extracted with ethyl acetate which was dried over $Na_2SO_4$ and evaporated to afford 1.64 g (91%) of the desired product, mp: 59-61°C.

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64.

Found: C, 71.67; H, 11.68; N, 7.36.

Example 115

(3S,4S)-3-Hydroxy-4-tert-butoxycarbonylamino-5-cyclohexyl-1-pentene.

To the resultant compound from Example 114 (1.62 g, 8.84 mmol) in methylene chloride (20 mL) was added di-tert-butyldicarbonate (1.93 g, 8.84 mmol). The mixture was stirred for 14 h, diluted with ethyl acetate, washed sequentially with 0.5 M $H_3PO_4$, saturated $NaHCO_3$ solution and brine, then dried over $Na_2SO_4$ and evaporated to afford 2.51 g (100%) of the desired compound.

Example 116

(3S,4S)-1,3-Dihydroxy-4-t-butyloxycarbonylamino-5-cyclohexylpentane

The resultant compound from Example 115 (327.6 mg, 1.16 mmol) in tetrahydrofuran (THF, 3 mL) of 0°C was treated with 9-borabicyclo(3.3.1)nonane (4.6 mL, 2.3 mmol in THF). After 3 h at room temperature water (0.1 mL) then NaOH (280 mg, 7.0 mmol) in water (1 mL) then 30% $H_2O_2$ (0.70 mL, 6.9 mmol) were added and the mixture was heated at 50°C for 90 min. The mixture was concentrated, dissolved in ethyl acetate, washed with brine, dried over $Na_2SO_4$, evaporated and chromatographed on silica gel with 2% methanol in chloroform to give 351.1 mg (100%) of the desired compound as an oil. DCI-MS: (M+H) = 302.

Example 117

(3S,4S)-1-Mesyloxy-3-hydroxy-4-t-butyloxycarbonylamino-5-cyclohexylpentane

The resultant compound from Example 116 was reacted according to the procedure in Example 89 to give the desired compound. EI-MS: $M^+$ = 379.

Example 118

(3S,4S)-1-Azido-3-hydroxy-4-t-butyloxycarbonylamino-5-cyclohexylpentane

The resultant compound from Example 117 was reacted according to the procedure in Example 90 to give the desired compound. DCI-MS: (M+H) = 327.

Example 119

Boc-Phe-His Amide of (3S,4S)-1-Azido-3-hydroxy-4-amino-5-cyclohexylpentane

Using the procedure of Example 79 with the resultant compound from Example 118 gave the desired compound.

Anal. Calcd for $C_{31}H_{46}N_8O_5 \cdot 0.5\ H_2O$: C, 60.08; H, 7.64; N, 18.08.

Found: C, 60.35; H, 7.48; N, 17.75.

Example 120

1-Benzyloxycarbonylamino-2,3-propanediol

1-Amino-2,3-propanediol (15.2 g, 167 mmol) and NaOH (8.1 g, 204 mmol) in water (70 mL) at -10°C was treated dropwise with benzyl chloroformate (28.5 mL, 200 mmol) in ether (30 mL) over 20 min. The reaction was stirred at 0°C for 30 min then at room temperature for 2 h. The mixture was acidified with 2 M HCl and extracted with ethyl acetate which was washed with 0.5 M $H_3PO_4$ and brine, then dried over $Na_2SO_4$ and evaporated. Recrystallization of the residue from benzene afforded 16.59 g (44%) of the desired product as a white powder. NMR (300 MHz, $CD_3OD$, ppm): 3.12 (dd,1H), 3.28 (dd,1H), 3.50 (m,2H), 3.68 (m,1H), 5.08 (s,2H), 7.35 (m,5H).

Example 121

1-Methylamino-2,3-propanediol

Lithium aluminum hydride (7.20 g, 189 mmol) in tetrahdyrofuran (THF, 300 mL) was heated to reflux and the resultant compound from Example 120 (17.0 g, 75.5 mmol) in THF (150 mL) was added dropwise over 10 min. The mixture was relfuxed for 2 h, cooled, quenched sequentially with water (10 mL), 3 M NaOH (40 mL) and water (20 mL), then filtered and concentrated. The residue was dissolved in water which was washed with ether and evaporated. Bulb to bulb distillation of the residue afforded 2.0 g (25%) of the desired compound as an oil. NMR (300 MHz, $CDCl_3$, ppm): 2.45 (S,3H), 2.68 (dd,1H), 2.77 (dd,1H), 3.61 (dd,1H), 3.72 (dd,1H), 3.78 (M,1H).

Example 122

(N-Methyl-2,3-dihydroxypropylamino)carbonyl-(O-methyl) tyrosine methyl ester

To the resultant compound from Example 136 (1.53 g, 6.5 mmol) in dioxane (5 mL) at 0°C was added the resultant compound from Example 121 (0.684 g, 6.5

mmol). The reaction was stirred at 0°C for 1 h then at room temperature for 1 h, evaporated and chromatographed on silica gel with 5% methanol in chloroform to afford 1.855 g (84%) of the desired product as an oil. NMR (300 MHz, $CDCl_3$, ppm), 2.88, 2.89 (S,3H total), 3.05 (m,2H), 3.26-3.60 (m,5H), 3.73 (S,3H), 3.80 (S,3H), 4.70 (m,1H), 5.07 (broad t,1H), 6.83 (dd,1H), 7.02 (dd,1H).

## Example 123

## (N-Methyl-2,3-dihydroxypropylamino)carbonyl-(O-methyl)tyrosine

The resultant compound from Example 122 (114 mg, 0.355 mmol) in dioxane (4 mL) and water (2 mL) at 0°C was treated with LiOH monohydrate (42.0 mg, 1 mmol). After 90 min 2 M HCl (0.6 mL, 1.2 mmol) was added and the mixture was evaporated to a foam which was used without further purification; DCI-MS: $(M+H)^+$ = 327.

## Example 124

## (2R)-3-(N-Methyl-2,3-dihydroxypropylamino)-carbonyl-2-benzylpropionic Acid Benzyl Ester

Prepared according to the procedure for Example 95 from the resultant compounds of Example 121 and Example 57. NMR (300 MHz, $CDCl_3$, ppm), 3.00 (s,3H), 5.10 (m,2H), 7.10-7.40 (m,10H); EI-MS: $M^+$ = 385.

## Example 125

## (2R)-3-(N-Methyl-2,3-dihydroxypropylamino)carbonyl-2-benzylpropionic Acid

The resultant compound from Example 124 (200 mg, 0.523 mmol) and 10% Pd on carbon (200 mg) in methanol (10 mL) were stirred under a hydrogen atmosphere for 3 h. The reaction was filtered and evaporated to afford 148 mg (97%) of the desired product as an oil.

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot 0.25\ H_2O$:

C, 60.09; H, 7.23; N, 4.67.

Found: C, 59.76; H, 7.10; N, 4.45.

Example 126

Dimethylaminocarbonyl-(O-methyl)tyrosine Methyl Ester

Prepared from dimethyl amine and the resultant compound from Example 136 according to the procedure for Example 122.

Example 127

Dimethylaminocarbonyl-(O-methyl)-tyrosine

Prepared according to the procedure of Example 123 from the resultant compound of Example 126 with the modification that the product was isolated by pouring the reaction mixture into 2 M HCl and extracting with ethyl acetate which was dried over $Na_2SO_4$ and evaporated. EI-MS: $M^+ = 266$.

Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52.

Found: C, 58.44; H, 6.87; N, 9.95.

Example 128

3,3-Dimethylglutaric Acid Mono t-butyl Ester

3,3-Dimethylglutaric anhydride (455 mg, 3.2 mmol) in tetrahydrofuran (THF, 5 mL) was treated with sublimed potassium t-butoxide (395 mg, 3.5 mmol). After 30 min the solution was concentrated, poured into saturated $NaHCO_3$ solution and washed with ether. The aqueous phase was acidified to pH 4 with 0.5 M $H_3PO_4$ and extracted with chloroform which was dried over $Na_2SO_4$ and evaporated to afford 179 mg (26%) of the desired product as an oil. NMR (300 MHz, $CDCl_3$, ppm), 1.13 (s,6H), 1.47 (s,9H), 2.33 (s,2H), 2.45 (s,2H).

Example 129

(4-t-Butyloxycarbonyl-3,3-dimethyl)butanoyl-phenylalanine benzyl Ester

Prepared according to the procedure from Example 95 from the resultant compound from Example 128 and phenylalanine benzyl ester p-toluenesulfonic acid

salt. NMR (300 MHz, $CDCl_3$, ppm), 0.96 (s, 3H), 1.00 (s, 3H), 1.44 (s, 9H), 1.90 (d, 1H), 2.16 (d, 1H), 2.25 (d, 1H), 2.29 (d, 1H), 3.03 (dd, 1H), 3.17 (dd, 1H), 4.92 (m, 1H), 5.12 (d,1H), 5.16 (d,1H), 7.10-7.40 (m,10H).

Example 130

(4-t-Butyloxycarbonyl-3,3-dimethyl)butanoylpenylalanine

Using the procedure of Example 125 with the resultant compound of Example 129 gave the desired product as an oil. NMR (300 MHz, $CDCl_3$, ppm), 0.93 (s,3H), 0.99 (s,3H), 1.45 (s,9H), 1.77 (d,1H), 2.10 (d,1H), 2.19 (d,1H), 2.25 (d,1H), 3.02 (dd,1H), 3.33 (dd,1H), 4.72 (m,1H), 7.25 (m,5H).

Example 131

Dimethylaminocarbonyl (O-methyl)Tyr-His Amide of (3S,4S)-1-(3-Methylbutylcarbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

Using the procedure of Example 79 with the resultant compounds from Example 127 and Example 80 gave the desired compound.

Example 132

(N-Methyl-2,3-dihydroxypropylamino)carbonyl-(O-methyl)Tyr-His Amide of (3S,4S)-1-(3-Methylbutyl-carbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

Using the procedure of Example 79 with the resultant compounds from Example 122 and Example 80 gave the desired compound.

Example 133

(2R)-3-(N-Methyl-2,3-dihydroxypropylamino)carbonyl-2-benzylpropionyl-His Amide of (3S,4S)-1-(3-Methyl-butylcarbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

Using the procedure of Example 79 with the resultant compounds from Example 125 and Example 80 gave the desired compound.

Example 134

(4-t-Butyloxycarbonyl-3,3-dimethyl)butanoyl-Phe-His Amide of (3S,4S)-1-(3-Methylbutylcarbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

Using the procedure of Example 79 with the resultant compounds from Example 130 and Example 80 gave the desired compound.

Example 135

(4-Hydroxycarbonyl-3,3-dimethyl)butanoyl-Phe-His Amide of (3-Methylbutylcarbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane HCl Salt

The resultant compound from Example 134 was stirred in 4 M HCl/methanol for 1 h and then evaporated to provide the desired compound.

Example 136

$\alpha$-Isocyanato-L-(O-methyl)tyrosine

A suspension of (O-methyl)tyrosine methyl ester hydrochloride (6 g) in toluene (125 mL) was heated at 100°C while phosgene was bubbled into the reaction mixture. After 2 h the mixture became homogeneous and the phosgene was continued for an additional 15 min. The mixture was cooled and evaporated with several benzene chasers to provide the desired product.

Example 137

2-t-Butyloxycarbonylamino-1-cyclohexyl-3-hydroxy-6-methylheptane

To a stirred -78°C solution of L-Boc-cyclohexylalaninal (1.0 g, 3.9 mmol) in anhydrous tetrahydrofuran (THF, 25 mL) was added isoamyl magnesium bromide (24.4 mL of 0.8 M solution in THF) dropwise over the course of 5 min. The mixture was warmed to 0°C for 2 h and then quenched with $NH_4Cl$ (1.34 g, 25 mmol) in $H_2O$ (25 mL). The THF was evaporated and the aqueous phase was extracted with ether (3 x 40 mL). The combined organic phase was washed (brine), dried ($Na_2SO_4$), evaporated, and chromatographed on silica

gel eluting with ethyl acetate/hexane (15/85). Combination of selected fractions provided the less polar "S"-hydroxy diastereoamer (375 mg, 29%). Mass spectrum: $M^+ = 327$.

Example 138

Boc-Phe-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane.

The resultant compound of Example 137 (320 mg, 0.977 mmol) was dissolved in 25 mL of anhydrous 1 M HCl in methanol. After 12 h, evaporation of the solvent provided the corresponding deprotected amine hydrochloride (241 mg, 93%) which was used in the below coupling without further purification.

To a stirred -23°C solution of Boc-Phe-His-OH (82.4 mg) was added a solution of the above amine salt (54 mg) in dimethylformamide. Hydroxybenzotriazole (HOBT, 41.5 mg) N-methylmorpholine (21 mg), and N',N'-dicyclohexylcarbodiimide (DCC, 42.2 mg) were then added sequentially. After 2.5 h, the mixture was allowed to warm to room temperature for 16 h, at which time the mixture was filtered and evaporated to a residue which was partitioned between ethyl acetate and saturated $NaHCO_3$. The organic phase was then washed separately with saturated $NaHCO_3$ and brine. Drying ($Na_2SO_4$) and evaporation of the solvent provided the crude product. Chromatography on $SiO_2$ eluting with dichloromethane-methanol mixtures gave the desired compound (79 mg, 63%). Mass spectrum: $M^+ = 611$.

Example 139

Boc-His-Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

Following the procedure of Example 138, but replacing Boc-Phe-His-OH with Boc-His-OH, gave the desired compound in 47% yield.

### Example 140

### Cbz-D-Ala-Phe-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

Following the procedure of Example 138, but replacing Boc-Phe-His-OH with Cbz-D-Ala-Phe-OH and replacing the resultant compound of Example 137 with the resultant compound of Example 139 gave the desired product.

### Example 141

### D-Ala-Phe-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

The resultant compound of Example 140 (1.0 g) in glacial acetic acid (20 mL) was hydrogenated with 10% Pd/C (450 mg) at 55 p.s.i. $H_2$. After 3 h, the mixture was filtered and evaporated. The residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ for 30 min. The organic phase was washed (brine), dried ($Na_2SO_4$), filtered, and evaporated to give the desired compound in 84% yield.

### Example 142

### D-Ser-Phe-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

Following the procedures of Examples 140 and 141, but replacing Cbz-D-Ala-Phe-OH with Cbz-D-Ser-Phe-OH, gave the desired product in 39% yield.

### Example 143

### ($OCH_3$)Tyr-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

Following the procedures of Examples 140 and 141, but replacing Cbz-D-Ala-Phe-OH with Cbz-($OCH_3$)-Tyr, gave the desired product.

### Example 144

### (Imidazol-4-yl)acetyl-($OCH_3$)Tyr-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

Following the procedure of Example 138, but replacing Boc-Phe-His-OH with (imidazol-4-yl)acetic

acid, and replacing the salt derived from the resultant compound of Example 137 with the resultant compound of Example 143, gave the desired compound in 34% yield after recrystallization.

Example 145

(Imidazol-1-yl)acetyl-($OCH_3$)Tyr-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

The resultant compound of Example 143 (250 mg) in dry THF at 0°C was treated sequentially with 2 eq. N-methylmorpholine and 1 equivalent bromoacetyl bromide. After 1 h, imidazole (5 eq) was added. The mixture was warmed to room temperature for 6 h and then evaporated. Chromatography of the residue on silica gel (dichloromethane/isopropyl amine/methanol, 89:9:2) provided the desired product.

Example 146

N-(2,3-dihydroxypropyl)Gly-($OCH_3$)Tyr-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

Following the procedure of Example 145, but replacing imidazole with 1-amino-2,3-dihydroxypropane provided the desired product.

Example 147

4-t-Butyloxycarbonylamino-3-hydroxy-6-methyl-1-(4-methylvaleryl)amino-1-phenylheptane.

To a stirred 0°C solution of N-benzylvaleramide (600 mg, 2.92 mmol) in dry THF (20 ml) was added butyl lithium (4.17 ml of a 1.32 M solution in hexane). The solution was cooled to -78°C and a solution of the resultant product of Example 49 (300 mg, 1.31 mmol) in THF (6 ml) was added dropwise. Saturated $NH_4Cl$ (20 ml) and water (20 ml) was added 1.5 h later. Ether (75 ml) and 1 M $H_3PO_4$ (5 ml) were then added. The layers were separated, and the organic phase was washed with saturated $NaHCO_3$ (15 ml) and brine (15 ml). Drying and evaporating provided an oil which was chromatographed on 100 g $SiO_2$ with $CH_2Cl_2/CH_3OH$

mixtures to give 378 mg, 67% of the desired material. Mass spectrum: $M^+$ = 434.

Example 148

Boc-Phe-Ala Amide of 4-Amino-3-hydroxy-6-methyl-1-(4-methylvaleryl)amino-1-phenylheptane.

Following the deprotection procedure of Example 138 and using the resultant compound of Example 147 gave the corresponding hydrochloride which was coupled to Boc-Phe-Ala according to the procedures of Example 16. The desired compound was obtained in 98% yield.

Mass spectrum: $(M+H)^+$ = 653.

Anal. calcd.: C, 68.1; H, 8.7; N, 8.6. Found: C, 68.1; H, 9.0; 8.3.

Example 149

4-t-Butyloxycarbonylamino-1-cyclohexyl-3-hydroxy-6-methyl-1-(4-methylvaleryl)aminoheptane

The resultant compound of Example 147 (70.0 mg, 0.161 mmol) in glacial acetic acid (15 ml) was hydrogenated over Pt black (70 mg) for 22 h. The mixture was filtered, diluted with $H_2O$ (50 ml) and brine (50 ml), and extracted with ether (50 ml). The organic phase was washed with water (2 x 50 ml), saturated $K_2CO_3$ (25 ml), and brine (10 ml). Drying ($MgSO_4$) and evaporating gave 54 mg of the desired material. Mass spectrum: $(M+H)^+$ = 441.

Anal. calcd.: C, 68.1; H, 11.0; N, 6.4.

Found: C, 68.3; H, 11.5; N, 6.3.

Example 150

Boc-Phe-Ala-amide of 4-Amino-1-cyclohexyl-3-hydroxy-6-methyl-1-(4-methylvaleryl)aminoheptane

Following the deprotection procedure of Example 138 and using the resultant compound of Example 149 gave the corresponding amine hydrochloride which was coupled to Boc-Phe-Ala according to the procedure of Example 16, the desired compound was obtained in 89%

yield. Mass spectrum: $M^+ = 658$.

Example 151

5-t-Butyloxycarbonylamino-4-hydroxy-7-methyl-2-phenyloctanoic Acid Isoamyl Amide

Using the procedure of Example 147, but replacing 4-methylvaleric benzamide with N-isoamyl phenylacetamide gave the desired compound in 15% after chromatography.

Example 152

Boc-Phe-Ala Amide of 5-Amino-4-hydroxy-7-methyl-2-phenyloctanoic Acid Isoamyl Amide

Following the deprotection procedure of Example 138 and using the resultant compound of Example 151 gave the corresponding amine hydrochloride which was coupled to Boc-Phe-Ala according to the procedure of Example 16. The desired compound was obtained in 75% yield. Mass spectrum: $M^+ = 652$.

Anal. calcd. for $C_{37}H_{56}N_4O_6$: C, 68.1; H, 8.7; N, 8.6.

Found: C, 67.8; H, 8.7; N, 8.1.

Example 153

5-t-Butyloxycarbonylamino-2-cyclohexyl-4-hydroxy-7-methyloctanoicAcid Isoamyl Amide

The resultant compound of Example 151 was hydrogenated according to the procedure of Example 149 to give the desired compound in 68% yield.

Example 154

Boc-Phe-Ala Amide of 5-Amino-2-cyclohexyl-4-hydroxy-7-methyloctanoic Acid Isoamyl Amide

Following the deprotection of Example 138 and using the resultant compound of Example 153 gave the corresponding amine hydrochloride which was coupled to Boc-Phe-Ala according to the procedure of Example 16. The desired compound was obtained in 82% yield.

## Example 155

## 4-t-Butyloxycarbonylamino-3-hydroxy-6-methylheptanoic Acid Ethyl Ester

To diisopropylamine (7.7 g, 0.077 mol) in dry tetrahydrofuran (20 ml) cooled to -20°C under an argon atmosphere was added dropwise n-butllithium in hexane (1.46 M, 52.4 ml, 0.077 mol). The solution was stirred 15 min, the temperature lowered to -78°C and dry ethyl acetate (6.7 g, 0.077 mol) added dropwise while maintaining the temperature below -75°C. The solution was stirred 10 min and a precooled (-78°C) tetrahydrofuran solution of Boc-L-leucinal (11 g, 0.051 mol) was added. After 30 min, 2 M HCl (40 ml) was added and the mixture was slowly warmed to 10°C and extracted with ether (3 x 200 ml). The combined ethereal extract was washed with satd. sodium chloride (NaCl) and dried with magnesium sulfate ($MgSO_4$) and filtered. Evaporation of the filtrate in vacuo gave 14 g of crude product which was purified by flash column chromatography (20% ethylacetate in hexane). Obtained 6 g of Boc-Sta-OEt.

H' NMR (300 MHz, $CDCl_3$, ppm), 0.93 (d,6H), 1.27 (t,3H), 1.3-1.75 (m,3H), 1.44 (S,9H), 2.50 (m,2H), 3.35 (s,1H), 3.63 (br m,1H), 4.03 (br m,1H), 4.18 (q,2H), 4.75 (br d,1H).

## Example 156

## 4-t-Butyloxycarbonylamino-3-hydroxy-6-methylheptanoic Acid (Boc-Statine)

To 0.8 g of Boc-Sta-OEt in 24 ml of dioxane/water (2:1) was added 120 mg of lithium hydroxide at 0°C. After 10 min, the mixture was warmed to room temperature. After 1 h, the mixture was poured to a 10% solution of potassium bisulfate and extracted with ethyl acetate (3 x 100 ml). The combined organic phase was washed with a satd. NaCl solution and dried with $MgSO_4$ and filtered. Evaporation of the filtrate

in vacuo gave 0.7 g of a white solid. Recrystallization from ether/hexane, gave a solid with a m.p. of 117-118°C.

Example 157

Boc-Sta Amide of Benzyl Amine

To a solution of 340 mg of Boc-Sta in 25 ml of tetrahydrofuran at -20°C was added 183 uL (1.25 eq.) of N-methylmorpholine, followed by 216 uL (1.25 eq.) of isobutylchloroformate. The solution was stirred for 5 min at which time 300 uL (excess) of benzyl amine was added. After 15 min at -20°C, the solution was warmed to 0°C for 30 min. The solid was filtered and the filtrate was evaporated in vacuo. The residual oil was dissolved in ethyl acetate (50 ml) and washed with 10 ml of 10% potassium bisulfate solution. The aqueous phase was extracted with ethyl acetate (2 x 50 ml) and the combined ethyl acetate solution was washed with satd. NaCl solution and dried with $MgSO_4$. Evaporation in vacuo gave a colorless oil which upon purification by silica gel column chromatography (5% MeOH/95% $CH_2Cl_2$) gave 370 mg (82%) of pure product as a colorless oil. Mass spectrum: $M^+$ = 364 NMR (60 MHz, $CDCl_3$, ppm); 0.95 (d,6H), 1.45 (S,9H), 1.35-1.55 (m,3H), 2.4 (d,2H), 3.4-4.4 (m,5H), 4.8 (br d,1H), 6.9 (br d,1H), 7.25 (s,5H).

Example 158

Boc-Sta Amide of Isobutylamine

Using the procedure of Example 157, but replacing benzylamine with isobutylamine gave the desired compound (87% yield). Mass spectrum: $M^+$ = 330.

Example 159

Boc-Sta Amide of Isopentylamine

Using the procedure of Example 157, but replacing benzylamine with isopentylamine gave the desired compound (81% yield). Mass spectrum: $M^+$ = 344.

Example 160

Boc-Sta Amide of 2-Methylbutylamine

Using the procedure of Example 157, but replacing benzylamine with 2-methylbutylamine gave the desired compound (86% yield). Mass spectrum: $M^+$ = 344.

Example 161

Boc-Sta Amide of Isoleucinol

Using the procedure of Example 157, but replacing benzylamine with isoleucinol gave the desired compound (85% yield). Mass spectrum: $M^+$ = 374.

Example 162

Boc-Sta Amide of Methioninol

Using the procedure of Example 157, but replacing benzylamine with methioninol gave the desired compound (83% yield). Mass spectrum: $M^+$ = 392.

Example 163

Amine Hydrochloride of Boc-Sta Amide of Benzyl Amine

Boc-Sta amide of benzylamine (100 mg, 0.27 mmol) was dissolved in 3 ml of 4N HCl and stirred for 10 min. The solvent was evaporated in vacuo and the crude product, the amine hydrochloride from deprotection of the N-terminal of Boc-Sta-amide of benzylamine was dried under high vacuum for 12 h at room temperature. Likewise, the amine hydrochloride of the compounds in Example 158 to Example 161 are prepared by the same procedure.

Example 164

Boc-Phe-His-Sta Amide of Benzylamine

To the amine hydrochloride of Boc-Sta amide of benzylamine (200 mg, 0.34 mmol) in 4 ml of dimethyl formamide (DMF) was added triethylamine (47 uL, 0.34 mmol). The solution was cooled to 0°C and Boc-Phe-His-OH was added (136 mg, 0.34 mmol), followed by 1-hydroxybenzotriazole (70 mg, 0.51 mmol) and then dicyclohexylcarbodiimide (72 mg, 0.34 mmol). The

solution was stirred at 0°C for 8 h and then at room temperature for 4 h. The solution was filtered and the solvent was evaporated under vacuum. The residual solid was dissolved in ethyl acetate (50 ml) and washed with satd. sodium bicarbonate and then satd. sodium chloride solution, dried with $MgSO_4$, filtered and the solvent evaporated in vacuo. The crude product was purified by silica gel column (8% MeOH:92% $CH_2Cl_2$) and 110 mg (50%) of product was obtained. m.p. 169°-170°C. Mass spectrum: $M^+ = 648$.

Anal. calcd. for $C_{35}H_{48}N_6O_6$: C, 64.79; H, 7.46; N, 12.95.

Found: C, 64.56; H, 7.40; N, 12.81.

Example 165

Boc-( α-Naphthyl)-Ala-Ala-Sta Amide of Benzylamine

To the amine hydrochloride of Boc-Sta amide of benzylamine (100 mg, 0.34 mmol) in THF (3 ml) was added triethylamine (47 uL, 1 equivalent). This solution was added to the mixed anhydride of Boc-(α -Naphthyl)Ala-Ala-OH generated at -20°C in the following manner: To Boc-( α-Naphthyl)Ala-Ala-OH (130 mg, 0.34 mmol) in 7 ml of THF at -20°C was added N-methylmorpholine (0.34 mmol), followed by isobutylchloroformate (0.34 mmol). The generation of the mixed anhydride was complete in 5-10 min. The reaction mixture was stirred at -20°C for 2 h then at 0°C for 30 min. It was poured into a 10% solution of potassium bisulfate (40 ml) and extracted with ethyl acetate (50 ml x 3). The combined ethyl acetate solution was washed with satd. sodium bicarbonate (40 ml) and then brine (40 ml), dried with $MgSO_4$, and filtered. The solvent was evaporated in vacuo. The residual oil was purified by silica gel column (5% MeOH:95% $CH_2Cl_2$) to give 140 mg of product (65% yield). m.p. 95°-96°C. Mass spectrum: $(M + H)^+ = 699$.

Example 166

Boc-Phe-His-Sta Amide of Isobutylamine

Using the procedure of Example 164, but using the amine hydrochloride of Boc-Sta amide of isobutylamine gave the desired compound (60% yield). m.p. 163-164°C. Mass spectrum: $(M+H)^+ = 615$.

Example 167

Boc-( α-Naphthyl)Ala-Ala-Sta Amide of Isoleucinol

Using the procedure of Example 165, but using the amine hydrochloride of Boc-Sta amide of isoleucinol gave the desired compound (81% yield). m.p. 181-182°C. Mass spectrum: $(M+H)^+ = 643$.

Example 168

Boc-( α-Naphthyl)Ala-Ala-Sta Amide of Methioninol

Using the procedure of Example 165, but using the amine hydrochloride of the Boc-Sta amide of methioninol gave the desired product (76% yield). m.p. 183-184°C. Mass spectrum: $(M+H)^+ = 661$.

Example 169

Boc-His-Sta Amide of 2-Methylbutylamine

Using the procedure of Example 164, but using the amine hydrochloride of Boc-Sta amide of 2-methylbutylamine and replacing Boc-Phe-His with Boc-His-OH gave the desired compound (60% yield). m.p. 115-116°C. Mass spectrum: $M^+ = 681$.

Example 170

t-Butylacetyl-Phe-His-Sta Amide of 2-Methylbutylamine

Using the procedure of 165, but using the amine hydrochloride of Example 169 and replacing Boc( -Naphthyl)-Ala-Ala-OH with t-butylacetyl-Phe-OH gave the desired compound (45% yield). m.p. 186-188°C. Mass spectrum: $(M+H)^+ = 627$.

Example 171

Boc-p-iodo-Phe-His-Sta Amide of 2-Methylbutylamine

Using the procedure of Example 165, but using the amine hydrochloride of Example 169 and replacing

Boc(α-Naphthyl)-Ala-Ala-OH with Boc-p-iodo-Phe-OH gave the desired compound (65% yield). m.p. 213°C (decomp.). Mass spectrum: $(M+H)^+ = 755$.

Example 172

4-t-Butyloxycarbonylamino-5-phenyl-3-hydroxypentanoic Acid Ethyl Ester (Boc-F-Sta Ethyl Ester)

Using the procedure of Example 155, but replacing Boc-L-leucinal with Boc-L-phenylalaninal gave the desired compound (52% yield). Mass spectrum: $M^+ = 337$.

Example 173

4-t-Butyloxycarbonylamino-5-phenyl-3-hydroxypentanoic Acid (Boc-F-Sta)

Using the procedure of Example 156 but using the compound in Example 172 gave the desired compound (95% yield). m.p. 88°C.

Example 174

Boc-F-Sta Amide of Isopentylamine

Using the procedure of example 157, but replacing Boc-Sta with Boc-F-Sta and replacing benzylamine with isopentylamine gave the desired compound (75% yield). m.p. 157-158°C. Mass spectrum: $M^+ = 378$.

Example 175

Boc-Phe-His-F-Sta Amide of Isopentylamine

Using the procedure of Example 164, but using the amine hydrochloride of Boc-F-Sta amide of isopentylamine gave the desired compound (51% yield). m.p. 201-202°C. Mass spectrum: $(M+H)^+ = 663$.

Example 176

4-t-Butyloxycarbonylamino-3-hydroxy-5-cyclohexylpentanoic Acid Ethyl Ester (Boc-ACHPA Ethyl Ester)

Using the procedure of Example 155, but replacing Boc-Leucinal with Boc-Cyclohexylalaninal gave the desired compound in 40% yield. Mass spectrum:

$M^+$ = 343.

Example 177

4-t-Butyloxycarbonylamino-3-hydroxy-5-cyclohexylpentanoic Acid (Boc-ACHPA)

Using the procedure of Example 156, but using the compound from Example 176, gave the desired compound (100% yield). Mass spectrum: $M^+$ = 315.

Example 178

Boc-ACHPA Amide of Isopentylamine

Using the procedure of Example 157, but replacing Boc-Sta with Boc-ACHPA and benzyl amine with isopentylamine gave the desired compound (70% yield). Mass spectrum: $M^+$ = 384.

Example 179

Boc-Phe-His-ACHPA Amide of Isopentylamine

Using the procedure of Example 164, but using the amine hydrochloride of Boc-ACHPA amide of isopentylamine gave the desired compound (42% yield). m.p. 108-110°C. Mass spectrum: (M + H) = 669.

Example 180

4-t-Butyloxycarbonylamino-2-benzyloxy-3-hydroxy-5-cyclohexylpentanoic Acid Methyl Ester

Using the procedure of Example 155, but replacing Boc-leucinal with Boc-cyclohexylalaninal, and replacing ethyl acetate with benzyloxymethyl acetate gave the desired compound in 14.5% yield. Mass spectrum: $M^+$ = 435.

Example 181

4-t-Butyloxycarbonylamino-2-benzyloxy-3-hydroxy-5-cyclohexylpentanoic Acid

Using the procedure of Example 156, but using the compound from Example 180 gave the desired compound (100% yield). Mass spectrum: $M^+$ = 431.

Example 182

4-Boc-amino-2-benzyloxy-3-hydroxy-5-cyclohexyl-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 157, but replacing Boc-Sta with the compound in Example 181 and benzyl amine with 2-methylbutylamine gave the desired compound (72% yield). Mass spectrum: $M^+ = 490$.

Example 183

4-Boc-amino-2,3-dihydroxy-5-cyclohexyl-pentanoic Acid Amide of 2-Methylbutylamine

A solution of 400 mg of the compound in Example 182 in 20 ml of methanol with 200 mg of palladium black added was stirred vigorously under 3 atmosphere of hydrogen for 17 h. The catalyst was filtered off and the solution was concentrated in vacuo. The crude product was purified by silica gel chromatography to give 203 mg (62% yield) of desired product. Mass spectrum: $M^+ = 400$.

Example 184

Amine Hydrochloride of 4-Boc-amino-2-benzyloxy-3-hydroxy-5-cyclohexyl-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 163, but replacing Boc-Sta amide of benzylamine with the compound is Example 182 gave the desired product (100% yield).

Example 185

Amine Hydrochloride of 4-Boc-amino-2,3-dihydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure in Example 163 but replacing Boc-Sta amide of benzylamine with the compound in Example 183 gave the desired product (100% yield).

Example 186

Boc-Phe-Alaninyl-4-amino-2-benzyloxy-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 165, but

replacing Boc-( α-Naphthyl)-Ala-Ala-OH with Boc-Phe-Ala-OH and using the amine hydrochloride in Example 184 gave the desired product (59% yield). Mass spectrum: $(M+H)^+ = 709$.

Example 187

Boc-Phe-Histidinyl-4-amino-2-benzyloxy-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 166, but using the amine hydrochloride in Example 184 gave the desired product (40% yield). Mass spectrum: $(M+H)^+ = 776$.

Example 188

Boc-Phe-Alaninyl-4-amino-2,3-dihydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 165, but replacing Boc-(α -Naphthyl)-Ala-Ala-OH with Boc-Phe-Ala-OH and using the amine hydrochloride in Example 185 gave the desired product. Mass spectrum: $(M+H)^+ = 619$.

Example 189

Boc-Phe-Histidinyl-4-amino-2,3-dihydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure in Example 165, but using the amine hydrochloride in Example 185 gave the desired product (35% yield). Mass spectrum: $(M+H)^+ = 685$.

Example 190

4-t-Butyloxycarbonylamino-2-methoxy-3-hydroxy-5-cyclohexylpentanoic Acid Ethyl Ester

Using the procedure of Example 155 but replacing Boc-Leucinal with Boc-cyclohexylalaninal, and replacing ethyl acetate with methoxy ethyl acetate gave the desired product (33% yield). Mass spectrum: $M^+ = 407$.

Example 191

4-t-Butyloxycarbonylamino-2-methoxy-3-hydroxy-5-cyclohexylpentanoic Acid

Using the procedure of Example 156, but using

the compound from Example 190 gave the desired product (100% yield). Mass spectrum: $M^+$ = 379.

Example 192

4-Boc-amino-2-methoxy-3-hydroxy-5-cyclohexyl-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 157, but replacing Boc-Sta with the compound in Example 191 and benzyl amine with 2-methylbutylamine gave the desired product (80% yield). Mass spectrum: $(M+H)^+$ = 449.

Example 193

Amine Hydrochloride of 4-Boc-amino-2-methoxy-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 163, but replacing Boc-Sta amide of benzyl amine with the compound in Example 192 gave the desired compound (100% yield).

Example 194

Boc-Phe-Histidinyl-4-amino-2-methoxy-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 164, but using the amine hyrochloride in Example 193 gave the desired product (35% yield). Mass spectrum: $(M+H)^+$ = 699.

Example 195

4-t-Butyloxycarbonylamino-2-allyl-3-hydroxy-5-cyclohexylpentanoic Acid Ethyl Ester

Using the procedure of Example 155, but replacing Boc-Leucinal with Boc-cyclohexylalaninal, and replacing ethyl acetate with ethyl-4-pentenoate gave the desired product in 55% yield. Mass spectrum: $M^+$ = 383.

Example 196

4-t-Butyloxycarbonylamino-2-allyl-3-hydroxy-5-cyclohexylpentanoic Acid

Using the procedure of Example 156, but using the compound from Example 195 gave the desired compound

(100% yield). Mass spectrum: $M^+ = 355$.

Example 197

4-Boc-amino-2-allyl-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 164, but replacing Boc-Phe-His-OH with the compound in Example 196 and using 2-methylbutylamine instead of an amine hydrochloride gave the desired product (50% yield). Mass spectrum: $M^+ = 424$.

Example 198

Amine Hydrochloride of 4-t-Boc-amino-2-allyl-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 167, but replacing Boc-Sta amide of benzylamine with the compound in Example 59 gave the desired compound (100% yield).

Example 199

Boc-Phe-Histidinyl-4-amino-2-allyl-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 164, but using the amine hydrochloride in Example 199 gave the desired product (40% yield). Mass spectrum: $(M+H)^+ = 709$.

Example 200

Boc-Phe-Histidinyl-4-amino-2-propyl-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

A solution of 11 mg of the compound of Example 199 in methanol with 3 mg of 10% palladium on charcoal added was stirred vigorously under hydrogen atmosphere for 2 h at room temperature. The catalyst was filtered off and the filtrate concentrated to give a colorless oil. Purification by silica gel column chromatography gave 11 mg of pure product (100% yield). Mass spectrum: $(M+H)^+ = 711$.

Example 201

Boc-Phe-Methioninyl-4-amino-2-methoxy-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 165, but replacing Boc-( α-Naphthyl)-Ala-Ala-OH with Boc-Phe-Met-OH and using the amine hydrochloride in Example 193 gave the desired compound (80% yield). Mass spectrum: $(M+H)^+ = 693$.

Example 202

Boc-Phe-S-methylcysteinyl-4-amino-2-methoxy-3-hydroxy-5-cyclohexlpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 165, but replacing Boc-( α-Naphthyl)-Ala-Ala-OH with Boc-Phe-S-methylcysteine and using the amine hydrochloride in Example 193 gave the desired compound (63% yield). Mass spectrum: $(M+H)^+ = 679$.

Example 203

Boc-Phe-Alaninyl-4-amino-2-allyl-3-hydroxy-5-cyclohexylpentanoicAcid Amide of 2-Methylbutylamine

Using the procedure of Example 165, but replacing Boc-( α-Naphthyl)-Ala-Ala-OH with Boc-Phe-Ala-OH and using the amine hydrochloride in Example 198 gave the desired compound (56% yield). Mass spectrum: $(M+H)^+ = 643$.

Example 204

Boc-Phe-S-methylcysteinyl-4-amino-2-allyl-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 165, but replacing Boc-(α -Naphthyl)-Ala-Ala-OH with Boc-Phe-S-methylcysteine and using the amine hydrochloride in Example 198 gave the desired compound (52% yield). Mass spectrum: $(M+H)^+ = 689$.

Example 205

2-Benzyloxycarbonylamino-1,4-butanediol

To 15 g of N-benzyloxycarbonyl L-aspartic acid in 250 ml of tetrahydrofuran at 0°C was added two

equivalents of $BH_3 \cdot THF$ (1 M). The solution was stirred at 0°C for 30 min and then at room temperature for 3.5 h. The reaction was carefully quenched with cold water. The product was extracted with ethyl acetate (3 x 300 ml) and the combined organic phase washed with brine and dried with anhydrous $MgSO_4$. Filtration and concentration gave an oil which was purified by silica gel column chromatography (10% $MeOH/CH_2Cl_2$) to give 7.1 g of white solid. Mass spectrum: $M^+ = 239$.

Example 206

4-Hydroxyethyl-oxazolidin-2-one

To 1.1 g of the compound in Example 204 in 25 ml of DMF at 0°C was added 360 mg of sodium hydride (60% oil dispersion) portionwise. At the end of the addition, the suspension was stirred at 0°C for 2 h and then at room temperature overnight. The solvent was evaporated under reduced pressure. The crude oily product was purified by silica gel column chromatography (10% $MeOH/CH_2Cl_2$) to give 580 mg of white solid. m.p. 90-91°C. Mass spectrum: $M^+ = 131$.

Example 207

(Oxazolidin-2-one-4-yl)ethanal

To 520 mg of the product from Example 206 in 110 ml of $CH_2Cl_2$ was added 2.1 g of pyridinium dichromate. The suspension was stirred at room temperature overnight. The reaction mixture was filtered through a thightly packed layer of celite and concentrated under reduced pressure. The crude brown oil was purified by silica gel column chromatography (5% $MeOH/CH_2Cl_2$) to give 270 mg of pure aldehyde. Mass spectrum: $M^+ = 129$.

Example 208

4-[(1,3-Dithiolan-2-yl)methyl]oxazolidin-2-one

To a solution of 370 mg of the aldehyde from Example 207 in 30 ml of dichloromethane was added

0.48 ml of 1,2-ethanedithiol. To this solution at 0°C was added 2 drops of boron trifluoride-ether complex. The solution was stirred at 0°C for 10 min and then at room temperature for 20 min. TLC analysis showed no aldehyde was left. The solution was concentrated and the crude oily residue was purified by silica gel column chromatography ($CH_2Cl_2$/EtOAc 1:1) to give 270 mg of product. Mass spectrum: $M^+ = 205$.

Example 209

4-[(1',3'-Dithian-2'-yl)methyl]oxazolidin-2-one

Using the procedure of Example 208, replacing 1,2-ethanedithiol with 1,3-propane-dithiol gave the desired product (70%). Mass spectrum: $M^+ = 219$.

Example 210

4-[(1',3'-Dioxolan-2'-yl)methyl]oxazolidin-2-one

To 320 mg of the aldehyde from Example 207 in 25 ml of benzene was added 1 ml of ethylene glycol and 10 mg of p-toluenesulfonic acid. The solution was heated to reflux for 1 h and cooled to room temperature. It was washed with satd. sodium bicarbonate solution and extracted with ethyl acetate (3 x 50 ml). The organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (5% $MeOH/CH_2Cl_2$) gave 213 mg of the desired product. Mass spectrum: $M^+ = 173$.

Example 211

4-[(1',3'-Dioxan-2'-yl)methyl]oxazolidin-2-one

Using the procedure of Example 210, replacing ethylene glycol with 1,3-propanediol gave the desired product (53%). Mass spectrum: $M^+ = 187$.

Example 212

2-t-Butyloxycarbonylamino-

3-(1',3'-dithiolan-2'-yl)-propanol

To 360 mg of the product from Example 208 in

ethanol/water (25 ml/25 ml) was added 785 mg of barium hydroxide (2 equivalents). The suspension was heated to reflux for 16 h. Upon cooling to room temperature, the solid formed was filtered and washed with methanol. The solution was concentrated under reduced pressure. The residue was dissolved in 20 ml of dichloromethane. To this solution was added 1.5 equivalents of di-t-butyldicarbonate. After 2 h, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography ($CH_2Cl_2$/EtOAc 6.4) to give 430 mg of pure product. Mass spectrum: $M^+ = 279$.

Example 213

2-t-Butyloxycarbonylamino-
3-(1',3'-dithian-2'-yl)-propanol

Using 110 mg of the product from Example 209 and the procedure in Example 212 gave 90 mg of the desired product.

Example 214

2-Benzyloxycarbonylamino-
3-(1',3'-dioxolan-2'-yl)-propanol

To 200 mg of the oxazolidinone from Example HS-56 in dioxane/ water (15 ml/15 ml) was added 400 mg of barium hydroxide (2 equivalents). The suspension was heated to reflux for 3.5 h, at which time all the starting material was consumed. The suspension was cooled to room temperature and filtered. The solid was washed with methanol and the solution was concentrated under reduced pressure. The residue was dissolved in 10 ml of dichloromethane and 1.5 equivalents of N-(benzyloxycarbonyloxy)-succinimide was added. After 1 h, the solution was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (5% $MeOH/CH_2Cl_2$) to give 305 mg of the desired product. Mass spectrum: $M^+ =$ 281, m.p. 85-86°C.

Example 215

2-Benzyloxycarbonylamino-3-(1',3'-dioxan-2'-yl)-propanol

Using 300 mg of the product from Example 211 and using the procedure of Example 214 gave 280 mg of the desired product.

Example 216

3-hydroxy-4-t-Butyloxycarbonylamino-5-(1',3'-dithiolan-2'-yl)-pentanoic Acid Ethyl Ester

To a solution of 0.28 ml of DMSO in 15 ml of dichloromethane at -78°C was added 0.24 ml of oxalyl chloride. After 5 min, a solution of 430 mg of the product from Example 219 in 20 ml of dichloromethane was added. After stirring at -78°C for 20 min, 1.6 ml of triethylamine was added and the solution stirred for another 20 min. It was poured into a 10% aqueous solution of potassium hydrogen sulfate. After separation of the organic phase, the aqueous phase was extracted with dichloromethane (2 x 100 ml). The combined organic solution was washed with water (3 x 50 ml) and then saturated NaCl solution and then dried with anhydrous sodium sulfate. The solution was filtered and concentrated under reduced pressure. The residual oily product as dried under high vacuum for 2 h at room temperature. It was then dissolved in 15 ml of THF and added at -78°C to 2.75 equivalents of lithio ethyl acetate generated in the following manner: (To 0.59 ml of diisopropyl amine in 1.5 ml of THF at -78°C was added 1 equivalent of a hexane solution of n-butyl-lithium (1.6 M). After 15 min, 0.41 ml of dry ethyl acetate was added and the solution was stirred at -78°C for 20 min. After The reaction was quenched with 10% potassium hydrogen sulfate solution after 30 min.
The aqueous phase was extracted with ethyl acetate (3 x 100 ml) and the combined organic phase was dried with anhydrous $MgSO_4$). It was filtered and concentrated under reduced pressure to give a pale yellow oil

which was purified by silica gel column chromatography (20% EtOAc/80% $CH_2Cl_2$) to give 258 mg of the desired product. Mass spectrum: $M^+ = 365$.

Example 217

3-Hydroxy-4-t-butyloxycarbonylamino-5-(1',3'-dithian-2'-yl)-pentanoic Acid Ethyl Ester

Using the same sequence of reactions outlined in Example 216 and using 140 mg of the product from Example 213 as the starting material provided 57 mg of the desired product after silica gel column chromatography. ($CH_2Cl_2$/EtOAc 2:8). Mass spectrum: $M^+ = 379$.

Example 218

3-Hydroxy-4-benzyloxycarbonylamino-5-(1',3'-dioxolan-2'-yl)-pentanoic Acid Ethyl Ester

Using the same sequence of reactions outlined in Example 216 and using 270 mg of the product from Example 214 as the starting material gave 210 mg of the desired product after silica gel column chromatography ($CH_2Cl_2$/EtOAc 1:1). Mass spectrum: $M^+ = 333$.

Example 219

3-Hydroxy-4-benzyloxycarbonylamino-5-(1',3'-dioxan-2'-yl)-pentanoic Acid Ethyl Ester

Using the same sequence of reactions outlined in Example 216 and using 274 mg of the product from Example 215 as starting material gave 200 mg of the desired product after silica gel column chromatography ($CH_2Cl_2$/EtOAc 6:4). Mass spectrum: $M^+ = 347$.

Example 220

3-Hydroxy-4-t-butyloxycarbonylamino-5-(1',3'-dithiolan-2'-yl)-pentanoic Acid

To a solution of 250 mg of the product from Example 216 in 6 ml of dioxane/water (1:1) was added 1.2 equivalents of lithium hydroxide. The solution was stirred at room temperature for 30 min. The solution was acidified with 10% potassium hydrogen sulfate

solution and extracted with ethyl acetate (3 x 50 ml) dried with anhydrous $MgSO_4$ and filtered. The solution was concentrated under reduced pressure to afford 248 mg of a gummy white solid which is used without further purification. Mass spectrum: $M^+ = 337$.

Example 221

3-Hydroxy-4-t-butyloxycarbonylamino-5-(1',3'-dithian-2'-yl)-pentanoic Acid

Using the procedure described in Example 220 and using 50 mg of the product from Example 217 as starting material gave 49 mg of the desired product. Mass spectrum: $M^+ = 351$.

Example 222

3-Hydroxy-5-benzyloxycarbonylamino-5-(1',3'-dioxolan-2'-yl)-pentanoic Acid

Using the procedure described in Example 220 and using 200 mg of the product for Example 219 as the starting material gave 147 mg of the desired product. Mass spectrum: $M^+ = 305$.

Example 223

3-Hydroxy-5-benzyloxycarbonylamino-5-(1',3'-dioxan-2'-yl)-pentanoic Acid

Using the procedure described in Example 220 and using 200 mg of the product from Example 219 as the starting material gave 200 mg of the desired product. Mass spectrum: $M^+ = 319$.

Example 224

3-Hydroxy-4-t-butyloxycarbonylamino-5-(1',3'-dithiolan-2'-yl)-pentanoic Acid Amide of 2-Methylbutyl Amine

To a solution of 250 mg of the product from Example 220 in 30 ml of dry THF at -15°C was added 0.13 ml of N-methylmorpholine, followed by 0.155 ml of isobutylchloro-formate. After stirring for 10 min, 0.25 ml of (S)-2-methylbutylamine was added. The reaction was complete after 20 min and was poured into

10% potassium hydrogen sulfate solution and extracted with ethyl acetate (3 x 50 ml), dried with anhydrous $MgSO_4$ and filtered. The solution was concentrated under reduced pressure to give a pale yellow oil which was purified by silica gel column chromatography (2% $MeOH/CH_2Cl_2$) to give 200 mg of pure product. Mass spectrum: $M^+ = 406$.

Example 225

3-Hydroxy-4-t-butyloxycarbonylamino-5-(1',3'-dithian-2'-yl)-pentanoic Acid Amide of 2-methylbutylamine

Using the procedure described in Example 224 and using 50 mg of the product from Example 221 as the starting material gave 49 mg of the desired product after silica gel column chromatography (3% MeOH/$CH_2Cl_2$). Mass spectrum: $M^+ = 420$.

Example 226

3-Hydroxy-4-benzyloxycarbonylamino-5-(1',3'-dioxolan-2'-yl)-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 224 and using 147 mg of the product from Example 222 as the starting material gave 124 mg of the desired product after silica gel column chromatography (2% MeOH/$CH_2Cl_2$). Mass spectrum: $M^+ = 408$.

Example 227

3-Hydroxy-4-benzyloxycarbonylamino-5-(1',3'-dioxan-2'-yl)-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 224 and using 200 mg of the product from Example 223 as the starting material gave 190 mg of the desired product after silica gel column chromatography (2% MeOH/$CH_2Cl_2$). Mass spectrum: $M^+ = 422$.

Example 228

Amine Hydrochloride of 3-hydroxy-4-t-butyloxycarbonylamino-5-(1',3'-dithiolan-2'-yl)-pentanoic Acid Amide of 2-Methylbutylamine

To 0.2 g of the product from Example 224 was added 8 ml of 4N HCl in dioxane. The solution was stirred at room temperature for 30 min and the solvent was then removed under reduced pressure to give a gummy solid which was used without further purification.

Example 229

Amine Hydrochloride of 3-hydroxy-4-t-butyloxycarbonylamino-5-(1',3'-dithian-2'-yl)-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 228 and using the product from Example 225 gave the desired product which was used without further purification.

Example 230

3-Hydroxy-4-amino-5-(1',3'-dioxolan-2'-yl)-pentanoic Acid Amide of 2-Methylbutylamine

To 124 mg of the product from Example 226 in a 50 ml roundbottom flask was added 10 mg of 10% palladium on charcoal. To this was added carefully 10 ml of methanol. The suspension was stirred vigorously under a hydrogen atmosphere by attaching a 3-way stopcock with a hydrogen-filled balloon attached. Reaction was complete in 10 min as shown by the complete disappearance of the starting material on TLC analysis. The suspension was filtered and the catalyst was washed with 20 ml of methanol. The combined methanol solution was concentrated under pressure to give the desired product which was used without further purification.

Example 231

3-Hydroxy-4-amino-5-(1',3'-dioxan-2'-yl)-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 230 and using the product from Example 227 as the starting

material gave the desired product which was used without further purification.

Example 232

Boc-Phe-S-methylcysteinyl-[3-hydroxy-4-amino-5-(1',3'-dithiolan-2'-yl)]-pentanoic Acid Amide of 2-Methylbutylamine

To a solution of 57 mg of Boc-Phe-S-methyl-cysteine in 5 ml of THF at -15°C was added 0.017 ml of N-methylmorpholine, followed by 0.020 ml of isobutyl-chloroformate. After 10 min, a solution of the product from Example 228 (starting with 49 mg) in 5 ml of THF with 0.016 ml of N-methylmorpholine was added. After the solution was stirred at -15°C for 1 h, it was poured into 10% potassium hydrogen sulfate and extracted with ethyl acetate (3 x 50 ml), dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The crude product obtained was purified by silica gel column chromatography ($CH_2Cl_2$/EtOAc 3:7) to give 36 mg of product. Mass spectrum: $(M + H)^+$ = 671; m.p. = 144-145°C.

Example 233

Boc-Phe-S-methylcysteinyl-[3-hydroxy-4-amino-5-(1',3'-dithian-2'-yl)]-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 232 and using 57 mg of Boc-Phe-S-methyl-cysteine and the product from Example 229 (from 44 mg of starting material) gave 25 mg of the desired product after silica gel column chromatography ($CH_2Cl_2$/EtOAc 3:7). Mass spectrum: $(M+H)^+$ = 685.

Example 234

Boc-Phe-S-methylcysteinyl-[3-hydroxy-4-amino-5-(1',3'-dioxolan-2'-yl)]-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 232 and using 63 mg of Boc-Phe-S-methylcysteine, 40 mg of

the product from Example 230, gave 51 mg of the desired product after silica gel column chromatography (2% $MeOH/CH_2Cl_2$). Mass spectrum: $(M+H)^+ = 639$.

Example 235

Boc-Phe-S-methylcysteinyl-[3-hydroxy-4-amino-5-(1',3'-dioxan-2'-yl)]-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 232 and using 40 mg of Boc-Phe-S-methylcysteine, 40 mg of the product from Example 231 gave 40 mg of the desired product after silica gel column chromatography (2% $MeOH/CH_2Cl_2$). Mass spectrum: $(M+H)^+ = 653$.

Example 236

Ethoxycarbonyl-Phe-Leu-[3-hydroxy-4-amino-5-(1',3'-dioxan-2'-yl)]-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 232 and using 42 mg of the ethoxycarbonyl-Phe-Leu, 35 mg of the product from Example 231 gave 36 mg of product after silica gel column chromatography (2% $MeOH/CH_2Cl_2$). Mass spectrum: $(M+H)^+ = 621$.

Example 237

Boc-Phe-His-[3-hydroxy-4-amino-5-(1',3'-dithiolan-2'-yl)]-pentanoic Acid Amide of 2-Methylbutylamine

To a solution of 47 mg of Boc-Phe-His-OH in 5 ml of DMF at −15°C was added sequentially 45 mg of 1-hydroxybenzotriazole, 21 mg of ethyl dimethylamino-propyl carbodiimide. After 1 h at −15°C, a solution of 37 mg of the product from Example 228 in .3 ml of DMF was added. The solution was kept at −15°C for several hours and then at room temperature overnight. The solvent was removed under reduced pressure and the residue was washed with saturated sodium bicarbonate and extracted with ethyl acetate (3 x 50 ml), dried with anhydrous $MgSO_4$ and filtered. The solution was

concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (5% $MeOH/CH_2Cl_2$) to give 12 mg of product. Mass spectrum: $(M+H)^+ = 691$.

## Example 238

## 2(R,S)-(4-morpholinylcarbonylmethyl)-3-(1'-naphthyl)-propionic Acid

To 50 ml of absolute ethanol was added 2 g of sodium metal. The suspension was stirred vigorously until all the sodium dissolved and the evolution of hydrogen ceased. To this solution of sodium ethoxide was added a solution of 11.6 g of diethylsuccinate in 10.4 g of 1-naphthaldehyde. The solution was heated to reflux for 3 h, at which time it was cooled to room temperature and concentrated on the rotavap. The residue was dissolved in 320 ml of water and extracted 6 times with 100 ml portions of ether. The aqueous layer was acidified with 2N HCl and extracted with 2 x 300 ml of ether and dried with anhydrous magnesium sulfate. Evaporation of the solvent gave a yellow gummy solid which was hydrogenated to the saturated acid using Pd/C as catalyst. Coupling of the resulting saturated acid to morpholine using the mixed anhydride method described in Example 17 followed by ester hydrolysis using the procedure of Example 136 gave the desired acid. Mass spectrum: $(M+H)^+ = 328$.

## Example 239

## Boc-ACHPA-amide of 2-methylbutylamine

Using the procedure of Example 157, but replacing Boc-Sta with Boc-ACHPA and benzylamine with 2-methylbutylamine gave the desired compound (76% yield). Mass spectrum: $M^+ = 384$.

## Example 240

## Boc-His-ACHPA-amide of 2-methylbutylamine

Using the procedure of Example 164, but using the amine hydrochloride of Boc-ACHPA-amide of

2-methylbutylamine and replacing Boc-Phe-His with Boc-His-OH gave the desired compound (62% yield). Mass spectrum: $(M+H)^{+}$ = 522.

Example 241

2(R,S)-(4-morpholinylcarbonylmethyl)-3-(1'-naphthyl)-propionyl-His-ACHPA-amide of 2-methylbutylamine

Using the procedure of Example 164, but replacing Boc-Phe-His-OH with the product in Example 238, and using the amine hydrochloride of Example 240 gave the desired product (65% yield). Mass spectrum: $(M+H)^{+}$ = 719.

Example 242

2(R,S)-(4-morpholinylcarbonylmethyl)-3-(4'-methoxyphenyl)-propionic Acid

Using the procedure described in Example 238, but replacing 1-naphthaldehyde with anisaldehyde gave the desired compound. Mass spectrum: $M^{+}$ = 295.

Example 243

2(R,S)-(4-morpholinylcarbonylmethyl)-3-(4'-methoxyphenyl)-propionyl-His-ACHPA-amide of 2-methylbutylamine

Using the procedure of Example 164, but replacing Boc-Phe-His-OH with the product in Example 242, and using the amine hydrochloride of Example 240 gave the desired product (61% yield). Mass spectrum: $(M+H)^{+}$ = 699.

Example 244

(3,4-cis-dihydroxypyrrolidinylcarbonyl)-Phe-methyl Ester

A suspension of L-phenylalamine methyl ester hydrochloride (10 g) in toluene (~200 ml) was heated to 100°C while phosgene gas was bubbled into the reaction mixture. After approximately 2 h the mixture became homogeneous. The bubbling of phosgene was continued for 15 more minutes keeping the temperature at ~100°C. The toluene was then evaporated and the residue chased with benzene several times. The isocyanate from L-Phe-$OCH_3$

was then dissolved in ~100 ml of methylene chloride and 1.1 equivalent of 3-pyrroline (75% pure) was added dropwise at 0°C. After 15 min, the reaction mixture was washed with 0.5 N HCl and methylene chloride. The organic layer was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent gave 3-pyrrolinylcarbonyl-Phe-methyl ester which was cis-hydroxylated under the following conditions: 2.5 g of the 3-pyrrolinylcarbonyl-Phe-methyl ester was dissolved in 50 ml of THF and 1 ml of a 2.5% solution of $OsO_4$ in t-butanol was added, followed by 1.15 g of N-methylmorpholine-N-oxide. After 1 h, the solvent was evaporated and the residue dissolved in 150 ml of ethyl acetate and washed with dilute $Na_2SO_3$ solution, satd. $NaHCO_3$ solution and then dried with $MgSO_4$. Evaporation of the solvent gave a gummy solid which was purified by $SiO_2$ column chromatography (5% MeOH/$CH_2Cl_2$) to give the desired compound (65% yield). Mass spectrum: $M^+ = 308$.

## Example 245

## (3,4-cis-dihydroxypyrrolidinylcarbonyl)-Phe-OH

Using the procedure of Example 156 and replacing Boc-Sta-OEt with the compound from Example 244 gave the desired compound. Mass spectrum: $M^+ = 294$.

## Example 246

## (3,4-cis-dihydroxypyrrolidinylcarbonyl)-O-methyl-Tyr-methyl Ester

Using the procedure described in Example 244 and replacing L-phenylalanine methyl ester with L-O-methyl-tyrosine methyl ester gave the desired compound. Mass spectrum: $M^+ = 338$.

## Example 247

## (3,4-cis-dihydroxypyrrolidinylcarbonyl)-O-methyl-Tyr-OH

Using the procedure described in Example 156 and replacing Boc-Sta-OEt with the compound from

Example 92 gave the desired compound. Mass spectrum: $M^+ = 324$.

Example 248

Boc-S-methyl-cys-ACHPA-amide of 2-Methylbutylamine

Using the procedure described in Example 165, but replacing Boc-($\alpha$-Naphthyl)Ala-Ala-OH with Boc-S-methyl-Cys-OH and using the amine hydrochloride of the compound from Example 85 gave the desired compound. Mass spectrum: $(M+H)^+ = 502$.

Example 249

(3,4-cis-dihydroxypyrrolidinylcarbonyl)-Phe-S-methyl-cys-ACHPA-amide of 2-Methylbutylamine

Using the procedure described in Example 165 but replacing Boc($\alpha$-Naphthyl)-Ala-Ala-OH with the compound from Example 245 and the amine hydrochloride of the compound from Example 248 gave the desired compound. Mass spectrum: $(M+H)^+ = 678$.

Example 250

Boc-O-methyl-Ser-ACHPA-amide of 2-Methylbutylamine

Using the procedure described in Example 165, but replacing Boc-($\alpha$-Naphthyl)-Ala-Ala-OH with Boc-O-methyl-Ser-OH and using the amine hydrochloride of the compound from Example 239 gave the desired compound. Mass spectrum: $(M+H)^+ = 486$.

Example 251

(3,4-cis-dihydroxypyrrolidinylcarbonyl)-O-methyl-Tyr-O-methyl-Ser-ACHPA Amide of 2-Methylbutylamine

Using the procedure described in Example 165, but replacing Boc-($\alpha$-Naphthyl)-Ala-Ala-OH with the compound from Example 247 and using the amine hydrochloride of the compound from Example 250 gave the desired compound. Mass spectrum: $(M+H)^+ = 682$.

Example 252

[(4-Thiomorpholinyl)carbonyl]-Phe Methyl Ester

A suspension of L-phenylalamine methyl ester

hydrochloride (6 g) in toluene (125 ml) was heated to 100°C and phosgene gas was bubbled into the reaction mixture. After approximately 1.5 h, the mixture became homogeneous. The bubbling of phosgene was continued for 10 more min. The solvent was then evaporated and the residue chased with benzene several times. The residue was then dissolved in ~100 ml of methylene chloride and cooled to ~0°C, and 1.1 equivalent of thiomorpholine was added dropwise. After 10 min the solution was washed with 1N HCl and the organic layer was dried with $MgSO_4$. Evaporation of solvent gave 5.5 g of product. Mass spectrum: $M^+ = 308$.

Example 253

[(4-Sulphonylmorpholinyl)carbonyl]-Phe Methyl Ester

To 2 g of the product from Example 252 in 100 ml of methylene chloride was added 2.94 g of a meta-chloroperbenzoic acid at 0°C. After 30 min the solvent was evaporated and ether solution was washed with 10% sodium sulfite solution and then with satd. sodium bicarbonate several times. The organic layer was dried with $MgSO_4$ and evaporation of the solvent gave a white solid which was purified by silica gel column chromatography (20% EtOAc/80%/$CH_2Cl_2$) to give 2.10 g (95%) of pure product. Mass spectrum: $M^+ = 340$.

Example 254

[(4-sulfonylmorpholinyl)carbonyl]-Phe-OH

Using the procedure described in Example 156, but replacing Boc-Sta-OEt with the compound from Example 253 gave the desired compound.

Example 255

[(4-sulfonylmorpholinyl)carbonyl]-Phe-O-methyl-Ser-ACHPA-amide of2-Methylbutylamine

Using the procedure described in Example 165, but replacing Boc-($\alpha$-Naphthyl)Ala-Ala-OH with the product from Example 254 and using the amine hydrochloride of the compound from Example 250 gave the

desired compound (70% yield). Mass spectrum: $(M+H)^+$ = 694.

Example 256

N-(3-Methylbutyl)-4-hydroxy-5-t-butyloxycarbonylamino-6-cyclohexylhex-1-ene-2-carboxamide

A solution of N-(3-methylbutyl)-2-methylpropenamide (643 mg, 4.15 mmol) in 25 ml of dry tetrahydrofuran was cooled under an $N_2$ atmosphere to -78°C and treated dropwise with 3.28 ml (8.5 mmol) of n-butyllithium in hexane. The resulting solution was warmed to 0°C for 20 min, recooled to -78°C and treated with 6.2 ml (6.2 mmol) of chlorotitanium triisopropoxide in hexane. After again warming to 0°C for 5 min, the dark solution was recooled to -78°C treated with a solution of N-t-butyloxycarbonylcyclohexylalininal (670 mg, 2.3 mmol) in 5 ml of tetrahydrofuran, stirred for 5 min at -78°C, warmed to 0°C for 20 min and quenched with saturated aqueous ammoniun chloride. The resulting suspension was treated with ca. 50 ml of ether, stirred until the salts became white, extracted with two 100 ml portions of ether, dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was separated by flash column chromatography using 4:1 chloroform/ ethyl acetate to give 249 mg (26%) of the (4S,5S) product ($R_f$ .44), 292 mg (31%) of the (4R,5S) product ($R_f$ .36, 3:2 chloroform/ethyl acetate) and 184 mg (20%) of a ca. 1:1 mixture of the two products. Mass spectrum: $M^+$ = 410.

Example 257

N-Isobutyl-4-hydroxy-5-t-butyloxycarbonylamino-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 256, but replacing N-(3-methylbutyl)-2-methyl-propenamide with N-isobutyl-2-methylpropenamide gave a ca. 1:1 mixture of the (4S,5S) product ($R_f$ .39) and (4R,5S) product ($R_f$ .31, 3:2 chloroform/ethyl acetate) which were separated

by flash column chromatography using 3:1 chloroform/ ethyl acetate. Mass spectrum: $M^+$ = 396.

Example 258

N-Methyl-4-hydroxy-5-t-butyloxycarbonylamino-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 256, but replacing N-(3-methylbutyl)-2-methyl-propenamide with N,2-dimethylpropenamide gave a ca. 1:1 mixture of (4S,5S) product ($R_f$ .13) and (4R,5S) product ($R_f$ .08, 3:2 chloroform/ethyl acetate) in 61% yield which were partially separated by flash column chromatography using 3:2 chloroform/ethyl acetate. Mass spectrum: $M^+$ = 354.

Example 259

N-(2,2-Dimethyl-3-(N,N-dimethylamino)propyl)-4-hydroxy-5-t-butyloxycarbonylamino-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 256, but replacing N-(3-methylbutyl)-2-methylpropenamide with N-(2,2-dimethyl-3-(N,N-dimethylamino)propyl)-2-methyl-propenamide gave a ca. 1:1 mixture of (4S,5S) and (4R,5S) products ($R_f$ .39, 1:1 methanol/chloroform) in 77% yield which were separated from remaining starting material by preparative thin layer chromatography using 1:1 methanol/chloroform. Further separation of diastereomers was not feasible. Mass spectrum: $M^+$ = 453.

Example 260

N-(3-t-Butyloxycarbonylamino-2,2-dimethylpropyl)-4-hydroxy-6-cyclohexyl-5-triphenyl-methylaminohex-1-ene-2-carboxamide

A solution of N-t-butyloxycarbonyl-N'-2-methyl-propenoyl-2,2-dimethyl-1,3-propanediamine (270 mg, 1.0 mmol) in 10 ml of dry tetrahydrofuran was cooled under a $N_2$ atmosphere to -78°C, treated dropwise with 1.68 ml (3.0 mmol) of n-butyllithium in hexane, stirred at -78°C

for 5 min, warmed to 0°C for 30 min, recooled to -78°C and treated with 266 mg (0.67 mmol) of N-(triphenylmethyl)cyclohexylalaninal in 3 ml of tetrahydrofuran. After stirring at -78°C for 10 min, the resulting solution was treated with aqueous $NH_4Cl$, extracted with 40 ml of ether, washed with 10 ml of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. Pure product (51% yield), as a mixture of (4S,5S) and (4R,5S) diastereomers was obtained after flash column chromatography using 1.8:1 hexane/ethyl acetate ($R_f$ .51, 1:1 hexane/ethyl acetate). Mass spectrum: $(M+1)^+ = 668$.

## Example 261

## 5-t-Butyloxycarbonylamino-6-cyclohexyl-4-hydroxy-2-(N-(3-methylbutyl)carboxamido)hex-1-ene-1,2-oxide

A solution of the resultant (4S,5S) diastereomer of Example 256 (206 mg, 0.50 mmol) in 8 ml of dichloromethane was treated with 217 mg (1.0 mmol) of 3-chloroperoxybenzoic acid and allowed to stand at room temperature. After 18 h, the solution was diluted with 5 ml of ether, treated with 10% aqueous $Na_2S_2O_3$, stirred vigorously for 1.5 h, extracted with 25 ml of ether, washed sequentially with 3N NaOH and saturated brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a 1.1:1 mixture of (2R) ($R_f$ .49) and (2S) ($R_f$ .40, 3:2 chloroform/ethyl acetate) diastereomers, respectively, in 100% yield. The diastereomeric products were separated by flash column chromatography using 5.5:1 chloroform/ethyl acetate. For each isomer, mass spectrum: $M^+ = 426$.

## Example 262

## 5-t-Butyloxycarbonylamino-6-cyclohexyl-4-hydroxy-2-(N-isobutylcarboxamido)hex-1-ene-1,2-oxide

Using the procedure of Example 261, but replacing the compound from Example 256 with the resultant (4S,5S) diastereomer from Example 257 gave,

after flash column chromatography using 5:1 chloroform/ethyl acetate, the desired (2R) ($R_f$ .44) and (2S) ($R_f$ .37, 3:2 chloroform/ethyl acetate) diastereomeric products in 53% and 47% yields, respectively. For each isomer, mass spectrum: $M^+$ = 412.

Example 263

(4S,5S)-N-(3-Methylbutyl)-5-t-butyloxycarbonylamino-6-cyclohexylhexane-1,4-diol-2-carboxamide

Ammonia (ca. 10 ml) was condensed into a flask containing 10 ml of dry tetrahydrofuran precooled to -78°C. The resulting mixture was treated with ca. 30 mg of lithium metal, stirred at -78°C for 10 min, treated with a solution of the mixture of epoxides produced in Example 261 in 1 ml of tetrahydrofuran, stirred at -78°C for 6 min and cautiously poured into a rapidly stirred mixture of ether and saturated aqueous $NH_4Cl$. The organic layer was separated, dried over $MgSO_4$ and reduced *in vacuo*. Separation by flash column chromatography using 1.8:1 chloroform/ethyl acetate followed by 13:1 chloroform/methanol gave a 66% yield (78% based on recovered starting material) of the desired compound as an inseparable 1.5:1 mixture of diastereomers ($R_f$ .04, 3:2 chloroform/ethyl acetate). Mass spectrum: $(M+1)^+$ = 429.

Example 264

(4S,5S)-N-(3-Methylbutyl)-1-acetoxy-4-hydroxy-5-t-butyloxycarbonylamino-6-cyclohexylhexane-2-carboxamide

A solution of the resultant compound of Example 263 (40.2 mg, 0.094 mmol) in 0.3 ml of dry dichloromethane was treated sequentially with 14.5 uL (0.10 mmol) of triethylamine and 9.8 uL (0.10 mmol) of acetyl chloride. After being allowed to stir overnight, the mixture was partitioned between dichloromethane and water, dried over $Na_2SO_4$ and purified by flash

column chromatography using 24:1 chloroform/ methanol as eluent to give a quantitative yield of the desired compound as a mixture of diastereomers ($R_f$ .45, 12:1 chloroform/methanol).

Example 265

(2R,4S,5S)-N-Isobutyl-1-azido-5-t-butyloxycarbonylamino-6-cyclohexylhexane-2,4-diol-2-carboxamide

A solution of 51.0 mg (0.124 mmol) of the resultant (2R) diastereomer from Example 261, 24 mg (0.37 mmol) of sodium azide and 15 mg (0.28 mmol) of ammonium chloride in 7 ml of methanol was heated at reflux for 18 h. The resulting mixture was partitioned between chloroform and water, dried over $Na_2SO_4$ and reduced to give a 98% yield of the desired compound which was homogenous by tlc ($R_f$ .54, 3:2 chloroform/ ethyl acetate). Mass spectrum: $(M+1)^+ = 456$.

Example 266

(2S,3S,5S)-N-Isobutyl-2-t-butyloxycarbonylamino-1-cyclohexyl-7-methyloctane-3,5-diol-5-carboxamide

A solution of 21.4 mg (0.052 mmol) of the resultant (2R) diastereomer of Example 261 in 1 ml of dry tetrahydrofuran was cooled under a $N_2$ atmosphere to 0°C and treated with 0.13 ml (0.26 mmol) of isopropylmagnesium chloride in ether. After 45 min, the mixture was treated with saturated aqueous $NH_4Cl$, extracted with ether and dried over $MgSO_4$). Separation by flash column chromatography using 3:1 hexane/ethyl acetate gave a 25% yield (57% based on recovered starting material) of the desired compound ($R_f$ .30, 6:1 chloroform/ ethyl acetate). Mass spectrum: $(M+1)^+ = 457$.

Example 267

(4S,5S)-N-(3-Methylbutyl)-5-t-butyloxycarbonylamino-6-cyclohexylhexane-1,2,4-triol-2-carboxamide

A solution of 135 mg (0.33 mmol) of the (4S,5S) diastereomer from Example 256 in 4 ml of tetrahydrofuran

was treated sequentially with 170 ml (0.017 mmol) of osmium tetroxide in t-butanol and ca. 100 mg (0.7 mmol) of 4-methylmorpholine-N-oxide. After stirring for 24 h, the solution was diluted with 50 ml of ether, washed sequentially with five 4 ml portions of 10% $Na_2S_2O_3$, 4 ml of 1M HCl, 4 ml of $H_2O$ and 4 ml of saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Separation by flash column chromatography using 19:1 chloroform/methanol gave an 88% yield of the desired compound as a 1:1 mixture of diastereomers ($R_f$ .35, 12:1 chloroform/methanol). Mass spectrum: $M^+$ = 444.

## Example 268

### (4S,5S)-N-Isobutyl-5-t-butyloxycarbonylamino-6-cyclohexylhex-1-ene-3,4-diol-2-carboxamide

A solution of 173 mg (0.44 mmol) of the (4S,5S) diastereomer from Example 257 and 68 mg (0.52 mmol) of selenious acid in 4 ml of dioxane was heated at 70°C for 16 h and 95°C for 4 h. After cooling, filtration through Celite and separation by flash column chromatography using 7:3 chloroform/ethyl acetate gave a 50% yield of the desired compound ($R_f$ .25, 7:3 chloroform/ethyl acetate) as a 1:1 mixture of diastereomers. Mass spectrum: $M^+$ = 412.

## Example 269

### (4S,5S)-N-(3-Methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide hydrochloride

The (4S,5S) diastereomer from Example 256 (31.5 mg, 0.077 mmol) was treated with 0.5 ml of a 4 M solution of HCl in dioxane and allowed to stand at ambient temperature for 1 h. After removal of the solvent *in vacuo*, the residue was treated twice with 0.5 ml of anhydrous ether followed each time by removal of the solvent *in vacuo*. The crude amine hydrochloride was used without further purification.

Example 270

(4S,5S)-N-Isobutyl-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide hydrochloride

Using the procedure of Example 269 with the resultant (4S,5S) diastereomer of Example 257 gave the desired compound.

Example 271

(4S,5S)-N-Methyl-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide hydrochloride

Using the procedure of Example 269 with the resultant (4S,5S) diastereomer of Example 258 gave the desired compound.

Example 272

N-(2,2-Dimethyl-3-(N,N-dimethylamino)propyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide dihydrochloride

A solution of 45 mg (0.1 mmol) of the resultant compound of Example 259 in *ca*. 0.1 ml of absolute ethanol was treated with 0.6 ml of 4 M HCl in dioxane and allowed to stand at ambient temperature for 1.5 h. After removal of the solvent *in vacuo*, the residue was treated twice with 0.5 ml of anhydrous ether followed each time by removal of the solvent *in vacuo*. The crude diamine dihydrochloride was used without further purification.

Example 273

N-(3-t-Butyloxycarbonylamino-2,3-dimethylpropyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide acetic acid salt

A solution of 80.3 mg (0.12 mmol) of the resultant compound of Example 260 in *ca*. 1.5 ml of 1:1 acetic acid/ethanol was treated with 5 drops of $H_2O$ and allowed to stir at ambient temperature for 9 h. After concentration *in vacuo*, the residue was treated twice with benzene and once with ether followed each time by removal of the solvent *in vacuo*. The resulting

oil was digested twice with hexane, followed each time by decantation. Removal of the last traces of solvent gave the desired compound as a mixture of diastereomers which was used without further purification.

## Example 274

**(4S,5S)-N-(3-Methylbutyl)-1-acetoxy-5-amino-4-hydroxy-6-cyclohexylhexane-2-carboxamide hydrochloride**

Using the procedure of Example 269 with the resultant compound of Example 264 gave the desired compound.

## Example 275

**(2R,4S,5S)-N-Isobutyl-5-amino-1-azido-6-cyclohexylhexan-2,4-diol-2-carboxamide hydrochloride**

Using the procedure of Example 269 with the resultant compound of Example 265 gave the desired compound.

## Example 276

**(2S,3S,5S)-N-Isobutyl-2-amino-1-cyclohexyl-7-methyloctan-3,5-diol-5-carboxamide hydrochloride**

Using the procedure of Example 269 with the resultant compound of Example 266 gave the desired compound.

## Example 277

**(2S,4S,5S)-N-Isobutyl-4-amino-1-chloro-6-cyclohexylhexane-2,4-diol-2-carboxamide hydrochloride**

Using the procedure of Example 269 with the resultant (2R) diastereomer of Example 262 gave the desired compound.

## Example 278

**(4S,5S)-N-(3-Methylbutyl)-5-amino-6-cyclohexylhexane-1,2,4-triol-2-carboxamide hydrochloride**

Using the procedure of Example 269 with the resultant compound of Example 267 gave the desired compound as a mixture of diastereomers.

Example 279

(4S,5S)-N-Isobutyl-5-amino-6-cyclohexylhex-1-ene-3,4-diol-2-carboxamide hydrochloride

Using the procedure of Example 269 with the resultant compound of Example 268 gave the desired compound as a mixture of diastereomers.

Example 280

Boc-Phe-Ala amide of (4S,5S)-N-(3-methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

A solution of 39 mg (0.115 mmol) of Boc-Phe-Ala-OH and 13 uL (0.12 mmol) of 4-methylmorpholine in 0.5 ml of dichloromethane and 0.1 ml of dimethylformamide was cooled to -15°C and treated with 15 uL (0.12 mmol) of isobutyl chloroformate. After being allowed to stir for 5 min, the solution was treated with a mixture of 0.077 mmol of the resultant compound of Example 269 and 8.4 uL (0.077 mmol) of 4-methylmorpholine in 0.6 ml of 2:1 dimethylformamide/dichloromethane, and allowed to stir at -15 - 0°C for .5 h and at ambient temperature for 2 h. After dilution with ca. 10 ml of ethyl acetate; the solution was washed successively with 1 ml of 1 M HCl, 1 ml of $H_2O$, 1 ml of saturated aqueous $NaHCO_3$ and 1 ml of $H_2O$; dried over $MgSO_4$ and concentrated in vacuo. Separation by flash column chromatography using 2.5% methanol in chloroform gave 27 mg (56%) of the desired compound which was recrystallized from chloroform/hexane. Mass spectrum: $(M+H)^+ = 629$.

Example 281

Boc-Phe-Ala amide of (4S,5S)-5-amino-4-hydroxy-6-cyclohexyl-2-(N-(3-methylbutyl)carboxamidohex-1-ene-1,2-oxide

A solution of 11 mg (0.018 mmol) of the resultant compound of Example 280 and 13 mg (0.11 mmol) of 3-chloroperoxybenzoic acid in 0.5 ml of dichloromethane was allowed to stir at ambient temperature

overnight. The resulting solution was treated with 0.5 ml of 10% $Na_2S_2O_3$, allowed to stir for 1 h, diluted with 3 ml of ethyl acetate, extracted with aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography using 1-2% methanol in chloroform gave 7.6 mg (67%) of the desired compound as a ca. 1:1 mixture of diastereomers ($R_f$ .38, .41, 7.5% methanol in chloroform). Mass spectrum: $(M+H)^+ = 645$.

## Example 282

## Boc-Phe-His amide of (4S,5S)-N-(3-methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

A solution of 52 mg (0.13 mmol) of Boc-Phe-His-OH and 52 mg (0.39 mmol) of 1-hydroxybenzotriazole monohydrate in 0.6 ml of dimethylformamide was cooled to -23°C, treated with 25 mg (0.13 mmol) of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride, and allowed to stir for 1 h. A solution of 0.13 mmol of the resultant compound of Example 269 and 29 uL (0.26 mmol) of 4-methylmorpholine in 0.6 ml of dimethylformamide was subsequently added, and the resulting solution was stirred at -23°C for 3 h and at ambient temperature for 16 h. After dilution with 10 ml of ethyl acetate, the solution was washed sequentially with 1 ml of saturated aqueous $NaHCO_3$ and 1 ml of $H_2O$, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography using 10% methanol in chloroform gave 49 mg (55%) of the desired compound ($R_f$ .20, 10% methanol in chloroform) which was recrystallized from tetrahydrofuran/hexane, m.p. 178-180°C (dec). Mass spectrum: $M^+ = 694$.

## Example 283

## Boc-Phe-His amide of N-(2,2-dimethyl-3-(N,N-dimethylamino)propyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

A solution of 3.09 g (6.83 mmol) of the

resultant compound of Example 272, 2.75 g (6.83 mmol) of Boc-Phe-His-OH, and 3.27 g (24.2 mmol) of 1-hydroxybenzotriazole in 20 ml of dimethylformamide was treated with 750 uL (6.83 mmol) of 4-methylmorpholine, cooled to -23°C, and treated with 1.31 g (6.83 mmol) of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrocholoride. After being allowed to stir at -23°C for ca. 2 h and at ambient temperature for 14 h, the solution was diluted with ethyl acetate, washed sequentially with aqueous $NaHCO_3$ and $H_2O$, dried ($MgSO_4$) and concentrated in vacuo. Separation by flash column chromatography using 2% methanol/2% isopropylamine in chloroform gave a 58% yield of the desired compound ($R_f$ .10, 2% methanol/2% isopropylamine in chloroform) as a mixture of stereoisomers. Mass spectrum: $(M+H)^+$ = 738.

## Example 284

### Boc-Phe-His amide of (4S,5S)-N-(3-methylbutyl)-1-acetoxy-5-amino-4-hydroxy-6-cyclohexylhexane-2-carboxamide

Using the procedure of Example 282 with the resultant compound of Example 274 gave, after purification by flash column chromatography using 7.5-10% methanol in chloroform, a 67% yield of the desired compound ($R_f$ .26, 10% methanol in chloroform) as a mixture of diastereomers. Mass spectrum: $(M+H)^+$ = 755.

## Example 285

### Boc-Phe-His amide of (4S,5S)-N-(3-methylbutyl)-5-amino-6-cyclohexylhexan-1,4-diol-2-carboxamide

A solution of 40 mg (0.05 mmol) of the resultant compound of Example 284 in 0.3 ml of dioxane and 0.15 ml of $H_2O$ was treated with 7 mg of $LiOH \cdot H_2O$ and allowed to stir at ambient temperature for 3 h. The resulting solution was partitioned between ethyl acetate and $H_2O$, dried over $MgSO_4$, and concentrated in vacuo. Separation by flash column

chromatography using 15% methanol in chloroform gave the desired compound as a mixture of diastereomers. Mass spectrum: $(M+H)^+ = 713$.

Example 286

Boc-Phe-His Amide of (2R,4S,5S)-N-isobutyl-5-amino-1-azido-6-cyclohexylhexane-2,4-diol-2-carboxamide

Using the procedure of Example 283 with the resultant compound of Example 275 gave, after purification by flash column chromatography using 5% methanol in chloroform, a 72% yield of the desired compound ($R_f$ .23, 7.5% methanol in chloroform). Mass spectrum: $(M+H)^+ = 740$.

Example 287

(5N)-Boc-Phe-His amide of (2R,3S,5S)-N-isobutyl-6-cyclohexyl-1,5-diaminohexane-2,4-diol-2-carboxamide

A solution of 8.2 mg (0.011 mmol) of the resultant compound of Example 286, 2 uL (0.035 mmol) of glacial acetic acid, and ca. 5 mg of 10% palladium on carbon in 0.5 ml of methanol was stirred overnight under a $H_2$ atmosphere. After dilution with chloroform, the mixture was filtered through Celite, concentrated *in vacuo*, filtered through a plug of basic alumina using 1:1 methanol/ethyl acetate as an eluent, concentrated, dissolved in chloroform, filtered, and concentrated to give 7.9 mg (100%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+ = 714$.

Example 288

Boc-Phe-His amide of (2S,3S,5S)-N-isobutyl-2-amino-1-cyclohexyl-7-methyloctane-3,5-diol-5-carboxamide

Using the procedure of Example 283 with the resultant compound of Example 276 gave, after purification by flash column chromatography using 6% methanol in chloroform, an 85% yield of the desired compound ($R_f$ .16; 7.5% methanol in chloroform). Mass spectrum: $(M+H)^+ = 741$.

Example 289

Boc-Phe-His amide of (2S,4S,5S)-N-isobutyl-4-amino-1-chloro-6-cyclohexylhexane-2,4-diol-2-carboxamide

Using the procedure of Example 283 with the resultant compound of Example 277 gave, after purification by flash column chromatography using 7.5% methanol in chloroform, a 68% yield of the desired compound ($R_f$ .24, 7.5% methanol in chloroform). Mass spectrum: $(M+H)^+$ = 733, 735.

Example 290

Boc-Phe-Ala amide of (4S,5S)-N-(3-methylbutyl)-5-amino-6-cyclohexylhexan-1,2,4-triol-2-carboxamide

Using the procedure of Example 280 with the resultant compound of Example 278, gave, after purification by flash column chromatography using 5% methanol in chloroform, a 38% yield of the desired compound ($R_f$ .27, 7.5% methanol in chloroform) as a 1:1 mixture of diastereomers. Mass spectrum: $(M+H)^+$ = 663.

Example 291

Boc-Phe-His amide of (4S,5S)-N-isobutyl-5-amino-6-cyclohexylhex-1-ene-3,4-diol-2-carboxamide

Using the procedure of Example 283 with the resultant compound of Example 279 gave, after purification by flash column chromatography using 7.5-10% methanol in chloroform, the desired compound as a 1:1 mixture of diastereomers. Mass spectrum: $(M-H)^-$ = 695.

Example 292

Boc-His amide of (4S,5S)-N-(3-methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 282 but replacing Boc-Phe-His-OH with Boc-His-OH gave, after purification by flash column chromatography using 7.5% methanol in chloroform, a 76% yield of the desired compound ($R_f$ .21, 7.5% methanol in chloroform), m.p.

97-99°C. Mass spectrum: $(M+H)^+ = 548$.

Example 293

His amide of (4S,5S)-N-(3-methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide dihydrochloride

Using the procedure of Example 272 with the resultant compound of Example 292 gave the desired compound.

Example 294

Boc-6-aminohexanoic acid

A mixture of 3.0 g (0.02 mol) of 6-aminohexanoic acid, 5.04 g (0.02 mol) of di-t-butyldicarbonate and 3.84 g (0.05 mol) of $NaHCO_3$ in 160 ml of 1:1 $H_2O$/tetrahydrofuran was stirred vigorously for 24 h. After concentration of the solvent, the mixture was acidified with HCl, saturated with NaCl, extracted with ethyl acetate, dried over $MgSO_4$ and concentrated in vacuo to give the desired product ($R_f$ 0.48, 9:1 chloroform/methanol).

Example 295

Boc-6-aminohexanoyl-Phe benzyl ester

A solution of 1.50 g (6.5 mmol) of the resultant compound of Example 294, 2.77 g (6.5 mmol) of phenylalanine benzyl ester p-toluenesulfonate salt, 0.87 g (6.5 mmol) of 1-hydroxybenzotriazole hydrate, 1.19 ml (8.4 mmol) of triethylamine and 1.74 g (8.4 mmol) of dicyclohexylcarbodiimide in 150 ml of tetrahydrofuran was allowed to stir at ambient temperature for 18 h. After concentration in vacuo, the residue was taken up in 300 ml of ethyl acetate, filtered, washed consecutively with 1 M HCl, $H_2O$, saturated $NaHCO_3$, $H_2O$ and saturated NaCl; dried over $MgSO_4$ and concentrated. Purification by flash column chromatography using 4:1 chloroform/ethyl acetate gave 2.35 g (77%) of the desired compound ($R_f$ 0.21, 4:1 chloroform/ethyl acetate).

Example 296

Boc-6-aminohexanoyl-Phe-OH

A mixture of 0.5 g (1.07 mmol) of the resultant compound of Example 295 and 30 mg of 10% palladium on carbon in 50 ml of methanol was stirred under an $H_2$ atmosphere for 3.5 h. After filtration through Celite, concentration in vacuo gave the desired compound.

Example 297

Boc-6-aminohexanoyl-Phe-His amide of (4S,5S)-N-(3-methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 283 with the resultant compound of Example 293 but replacing Boc-Phe-His-OH with Boc-6-aminohexanoyl-Phe-OH gave, after purification by flash column chromatography using 7.5% methanol in chloroform, the desired compound ($R_f$ .20, 10% methanol in chloroform). Mass spectrum: $(M+H)^+$ = 808.

Example 298

6-Aminohexanoyl-Phe-His amide of (4S,5S)-N-(3-methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide bis trifluoroacetate

A solution of the resultant compound of Example 297 (17 mg, 0.021 mmol) in 0.2 ml of trifluoroacetic acid was allowed to stand at ambient temperature for 40 min. After removal of the solvent in vacuo, and the residue was treated three times with 0.5 ml of ether and concentrated in vacuo to give the desired compound as a white solid. Mass spectrum: $(M+H)^+$ = 708.

Example 299

t-Butylacetyl-Phe-His amide of N-(3-t-butyloxycarbonylamino-2,2-dimethylpropyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 283 with the resultant compound of Example 273 but replacing Boc-Phe-His-OH with t-butylacetyl-Phe-His-OH gave, after

purification by flash column chromatography using 7.5% methanol in chloroform, a 32% yield of the desired compound as a mixture of diastereomers ($R_f$ .09, .11, 7.5% methanol in chloroform). Mass spectrum: $(M+H)^+$ = 808.

Example 300

(5N)-t-Butylacetyl-Phe-His amide of N-(3-amino-2,2-dimethylpropyl)-5-amino-6-cyclohexylhex-1-en-4-ol-2-carboxamide

Using the procedure of Example 272 with the resultant compound of Example 299 gave a white solid. Purification and neutralization by flash column chromatography using 7.5-10% methanol/2% isopropylamine in chloroform gave a 38% yield of the desired compound ($R_f$ .29, 10% methanol/2% isopropylamine in chloroform). Mass spectrum: $(M+H)^+$ = 708.

Example 301

(4S,5S,8R,10R,11S)-N-Isobutyl-6-aza-11-(t-butyloxycarbonylamino)-5-(cyclohexylmethyl)-4,10-dihydroxy-8-isobutyl-7-oxo-12-phenyldodec-1-ene-2-carboxamide

Using the procedure of Evans, et al. (J. Org. Chem. 1985, 50, 4615) with the resultant compound of Example 270 and (3R,5R,1'S)-5-(1-(t-butyloxycarbonylamino)-2-phenylethyl)-3-isobutyldihydrofuran-2-(3H)-one (D.J. Kempf, J. Org. Chem. 1986, 51, 3921) gave the desired compound after purification by column chromatography using 3:2 ethyl acetate:hexane. Mass spectrum: $(M+H)^+$ = 658.

Example 302

(4S,5S,8R,10S,11S)-N-Isobutyl-6-aza-11-(t-butyloxycarbonylamino)-5-(cyclohexylmethyl)-4,10-dihydroxy-7-oxo-8-(4-pentenyl)-12-phenyl-dodec-1-ene-2-carboxamide

Using the procedure of Evans, et al. (J. Org. Chem. 1985, 50, 4615) with the resultant compound of

Example 270 and (3R,5S,1'S)-5-(1-(t-butyloxycarbonylamino)-2-phenylethyl)-3-(4-pentenyl)dihydrofuran-2-(3H)-one (D.J. Kempf, J. Org. Chem. 1986, 51, 3921) gave the desired compound after purification by MPLC using 3:2 ethyl acetate:hexane. Mass spectrum: $(M+H)^+ = 670$.

Example 303

N-Methyl-N-(2-(N,N-dimethylamino)ethyl)carbamoyl-(O-methyl)tyrosine methyl ester

A solution of 0.5 g (2.1 mmol) of the resultant compound of Example 136 in 50 ml of dichloromethane was cooled to 0°C and treated with 0.3 ml (2.3 mmol) of N,N,N'-trimethylethylenediamine. After being allowed to stir for 16 h, the solution was concentrated and the desired compound was isolated by flash column chromatography using 1% methanol/2% isopropylamine in chloroform.

Example 304

N-Methyl-N-(2-(N,N-dimethylamino)ethyl)carbamoyl-(O-methyl)tyrosine lithium salt

A solution of the resultant compound of Example 303 in dioxane was cooled to 0°C, treated with 1.05 equiv. of aqueous lithium hydroxide (0.5 M) and stirred for 1.5 h. The resulting solution was concentrated *in vacuo* to give the desired compound as a white solid.

Example 305

N-Methyl-N-(2-(N,N-dimethylamino)ethyl)carbamoyl-(O-methyl)Tyr-His amide of (4S,5S)-N-(3-methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 283 but replacing Boc-Phe-His-OH with the resultant compound of Example 304 and replacing the resultant compound of Example 272 with the resultant compound of Example 293 gave the desired compound.

Example 306

5-Carbomethoxypentanoyl-(O-methyl)Tyr benzyl ester

Using the procedure of Example 280 but replacing Boc-Phe-Ala-OH with adipic acid monomethyl ester and replacing the resultant compound of Example 269 with (O-methyl)tyrosine benzyl ester hydrochloride gave the desired compound.

Example 307

5-Carbomethoxypentanoyl-(O-methyl)Tyr-OH

A solution of the resultant compound of Example 306 and 20% palladium on carbon in methanol was shaken under an $H_2$ atmosphere. After filtration, concentration of the solution *in vacuo* gave the desired compound.

Example 308

5-Carbomethoxypentanoyl-(O-methyl)Tyr-Leu benzyl ester

Using the procedure of Example 280 but replacing Boc-Phe-Ala-OH with the resultant compound of Example 307 and replacing the resultant compound of Example 269 with leucine benzyl ester p-toluenesulfonate salt gave, after purification by flash column chromatography using 20% ethyl acetate in chloroform, the desired compound in 64% yield.

Example 309

5-Carbomethoxypentanoyl-(O-methyl)Tyr-Leu-OH

A solution of the resultant compound of Example 308 and 20% palladium on carbon in methanol was shaken under an $H_2$ atmosphere. After filtration, concentration of the solution *in vacuo* gave the desired compound in 97% yield.

Example 310

5-Carbomethoxypentanoyl-(O-methyl)Tyr-Leu amide of N-(2,2-dimethyl-3-(N,N-dimethylamino)propyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 280 but replacing Boc-Phe-Ala-OH with the resultant compound of Example 309 and replacing the resultant compound of

Example 269 with the resultant compound of Example 272 gave, after purification by flash column chromatography using 1.25% methanol/1% isopropylamine/chloroform, the desired compound in 57% yield ($R_f$ 0.38 (2.5% methanol/ 2% isopropylamine/chloroform)).

Example 311

5-Carboxypentanoyl-(O-methyl)Tyr-Leu amide of N-(2,2-dimethyl-3-(N,N-dimethylamino)propyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

A solution of the resultant compound of Example 310 (319 mg, 0.41 mmol) in 10 ml of tetrahydrofuran was treated with a solution of 85 mg (2.0 mmol) of lithium hydroxide hydrate in 10 ml of $H_2O$ and allowed to stir at ambient temperature for 1 h. The resulting solution was neutralized to pH 7 with 1 M HCl, extracted with three 100 ml portions of chloroform, dried, and concentrated to give 268 mg (86%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+$ = 772.

Example 312

4-t-Butyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-cyclohexylpentanoic acidethyl ester.

To a solution of 8.0 g of Boc-cyclohexylalaninal in 125 ml of tetrahydrofuran at 10°C was added 10 ml of ethyl bromodifluoroacetate. The reaction flask was immersed in a sonicating bath. To this solution was added portionwise 6.18 g of zinc dust. After 30 min of sonication TLC check showed reaction was essentially complete. The reaction mixture was filtered through a tightly packed pad of Celite and the filtrate was concentrated. The residual oil was dissolved in methylene chloride and washed with 0.5 M potassium bisulfate. The organic layer was dried with anhydrous sodium sulfate, filtered and concentrated. Purification by silica gel column (20% ethyl acetate/80% hexane) provided 4.5 g of 3R isomer and 4.0 g of 3S isomer.

Mass spectrum: $M^+ = 379$.

Example 313

4(S)-t-butyloxycarbonylamino-2,2-difluoro-3R-hydroxy-5-cyclohexylpentanoic acid.

Using the procedure of Example 156, but replacing Boc-Sta-OEt with the product from Example 312 gave the desired product. Mass spectrum: $M^+ = 351$.

Example 314

4S-t-butyloxycarbonylamino-2,2-difluro-3R-hydroxy-5-cyclohexylpentanoic acid amide of 2-methylbutylamine.

Using the procedure of Example 157, but replacing Boc-Sta-OH with the product from Example 313 and replacing benzyl amine with 2-methylbutylamine gave the desired product (75% yield). Mass spectrum: $M^+ = 420$.

Example 315

Boc-Phe-His-4S-amino-2,2-difluoro-3R-hydroxy-5-cyclohexylpentanoic acid amide of 2-methylbutylamine.

Using the procedure of Example 164, but using the amine hydrochloride of the product in Example 314 gave the desired product (47% yield). Mass spectrum: $(M+H)^+ = 705$.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, heptonate, glycerophosphate, hemisulfate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, oxalate, 2-naphthalenesulfonate, pamoate, pectinate, persulfate,

3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl., and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

The novel compounds of the present invention possess an excellent degree of activity and specificity in treating renin-associated hypertension in a host. The ability of the compounds of the invention to inhibit human renal renin can be demonstrated in vitro by reacting a selected compound at varied concentrations with human renal renin, free from acid proteolytic activity, and with human renin substrate (angiotensinogen) at 37°C and pH 6.0. At the end of the incubation, the amount of angiotensin I formed is measured by radioimmunoassay and the molar concentration required to cause 50% inhibition, expressed as the $IC_{50}$, is calculated.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the

specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparation, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and

will therefore melt in the rectum and release the drug.

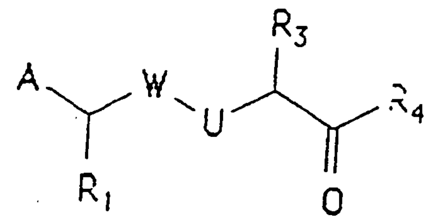
Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

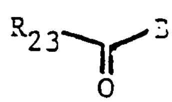
The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

WHAT IS CLAIMED IS:

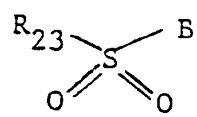
1. Compounds of the formula



wherein A is hydrogen; loweralkyl; arylalkyl; $OR_{20}$ or $SR_{20}$ wherein $R_{20}$ is hydrogen, loweralkyl or aminoalkyl; $NR_{21}R_{22}$ wherein $R_{21}$ and $R_{22}$ are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl;



and



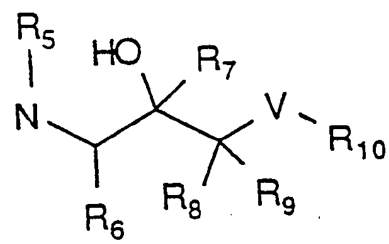
wherein B is NH, alkylamino, S, O, $CH_2$, $NHCH_2$ or CHOH and $R_{23}$ is loweralkyl, cycloalkyl, aryl, arylalkyl, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, [(dialkylamino)alkyl](alkyl)amino, (dihydroxyalkyl)(alkyl)amino, carboxyalkyl, aminoalkyl, N-protected aminoalkyl, alkylaminoalkyl, alkoxycarbonylalkyl, (N-protected)(alkyl)-aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl or a substituted or unsubstituted heterocyclic;

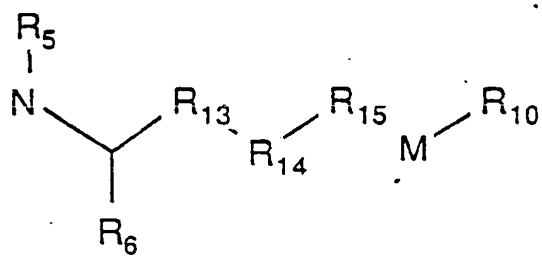
W is C=O or CHOH;

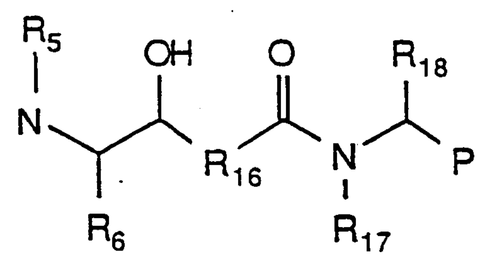
U is $CH_2$ or $NR_2$, provided that when W is CHOH then U is $CH_2$;

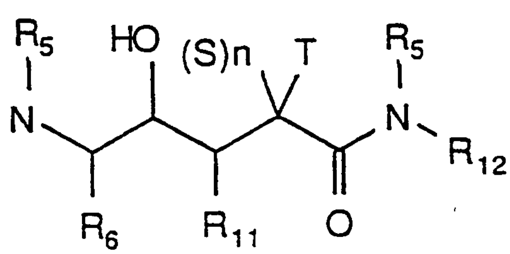
$R_1$ is loweralkyl, cycloalkylmethyl, benzyl, 4-methoxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazoyl)methyl, 4-hydroxybenzyl, $\alpha,\alpha$-dimethylbenzyl, 1-benzyloxyethyl,

phenethyl, phenoxy, thiophenoxy or anilino; provided if $R_1$ is phenoxy, thiophenoxy or anilino, B is $CH_2$ or CHOH or A is hydrogen; $R_3$ is loweralkyl, loweralkenyl, [(alkoxy)alkoxy]loweralkyl, (thioalkoxy)alkyl, benzyl or heterocyclic ring substituted methyl; $R_4$ is

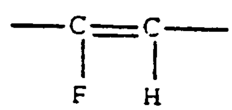


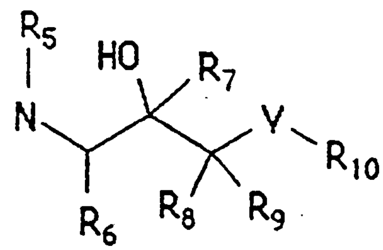
wherein $R_5$ is hydrogen or loweralkyl; $R_6$ is loweralkyl, cycloalkylmethyl, benzyl, or $CH_2R_{24}$, where $R_{24}$ is selected from 1,3-dioxan-2-yl; 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl or 1,3-dithian-2-yl; $R_7$, $R_8$ and $R_9$ are hydrogen or loweralkyl and may be the same or different; V is NH, O, S, SO, $SO_2$, or $CH_2$; $R_{10}$ is loweralkyl, cycloalkyl, cycloalkyl-alkyl, aryl, arylalkyl or an N-protecting group, or V and $R_{10}$ taken together are $N_3$; with the proviso that $R_{10}$ may be an N-protecting group only when V is NH; $R_{13}$ is CHOH or CO; $R_{14}$ is $CH_2$, $CF_2$ or CF with the proviso that when $R_{13}$ is CO, $R_{14}$ is $CF_2$; $R_{15}$ is $CH_2$, $CHR_{25}$ wherein $R_{25}$ is loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, or $R_{14}$ and $R_{15}$ taken together can be



with the proviso that when $R_{14}$ is $CF_2$, $R_{15}$ is $CH_2$; M is O, S, SO, $SO_2$, $NR_{26}$ wherein $R_{26}$ is hydrogen or loweralkyl, $NR_{27}SO_2$ or $NR_{27}CO$ wherein $R_{27}$ is hydrogen or loweralkyl, or M and $R_{10}$ taken together are $N_3$; $R_{16}$ is $CH_2$, $CF_2$ or $CHR_{45}$ where $R_{45}$ is loweralkyl, hydroxy, hydroxyalkyl, alkoxy, allyl, alkaryloxy or thioalkyl $R_{17}$ is hydrogen or loweralkyl; $R_{18}$ is loweralkyl or lipophilic or aromatic amino acid side chains; P is hydrogen, loweralkyl or $-CH_2OR_{28}$, wherein $R_{28}$ is hydrogen, loweralkyl or alkaryl; $R_{11}$ is hydrogen or hydroxy; n is 0 or 1; when n is 0, T is alkylidene or alkylidene oxide; when n is 1, S is hydrogen or hydroxy and T is loweralkyl, hydroxyalkyl, aminoalkyl, haloalkyl, or azidoalkyl; $R_{19}$ is hydrogen or loweralkyl; $R_{12}$ is hydrogen, loweralkyl, alkyl- cycloalkyl, arylalkyl,

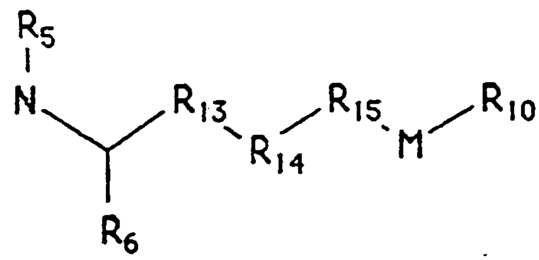
aminoalkyl, dialkylaminoalkyl; and pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1 wherein $R_4$ is



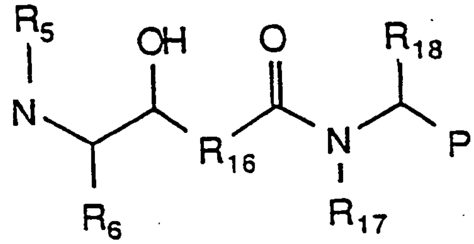
and $R_1$ is 1- or 2-naphthylmethyl, benzyl or 4-methoxybenzyl; $R_3$ is loweralkyl, imidazol-4-yl-methyl, pyrazolylmethyl, or thiomethoxymethyl; $R_5$, $R_7$, $R_8$ and $R_9$ are hydrogen; $R_6$ is isobutyl or cyclohexylmethyl; V is O, S, $SO_2$, $CH_2$ or NH; and $R_{10}$ is loweralkyl or cycloalkyl.

3. A compound according to Claim 1 wherein $R_4$ is



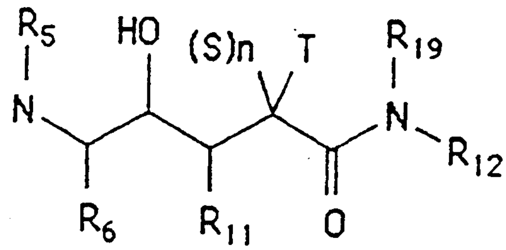
and $R_1$ is 1- or 2-naphthylmethyl, benzyl or 4-methoxybenzyl; $R_3$ is loweralkyl, imidazol-4-yl-methyl, pyrazolylmethyl, or thiomethoxymethyl; $R_5$ is hydrogen; $R_6$ is isobutyl or cyclohexylmethyl; $R_{13}$ is CHOH or C=O; $R_{14}$ is $CF_2$ or $CH_2$; $R_{15}$ is $CH_2$; M is S, $SO_2$ or NHC=O; and $R_{10}$ is loweralkyl or cycloalkyl.

4. A compound according to Claim 1 wherein $R_4$ is



and $R_1$ is 1- or 2-naphthylmethyl, benzyl or 4-methoxybenzyl; $R_3$ is loweralkyl, imidazol-4-yl-methyl, pyrazolylmethyl, or thiomethoxymethyl; $R_5$, $R_{17}$ is hydrogen; $R_{16}$ is $CH_2$; $R_6$ is isobutyl, cyclohexylmethyl or $CH_2R_{24}$, where $R_{24}$ is 1,3-dithiolan-2-yl; P is hydrogen or hydroxymethyl; and $R_{18}$ is loweralkyl.

5. A compound according to Claim 1 wherein $R_4$ is



and $R_1$ is 1- or 2-naphthylmethyl, benzyl or 4-methoxybenzyl; $R_3$ is loweralkyl, imidazol-4-yl-methyl, pyrazolylmethyl, or thiomethoxymethyl; $R_5$, $R_{11}$ and $R_{19}$ are hydrogen; $R_6$ is isobutyl or cyclohexylmethyl; and $R_{12}$ is loweralkyl, aminoalkyl or dialkylaminoalkyl.

6. A compound according to Claim 2 wherein A is (morpholin-4-yl)carbonyl-$CH_2$; $R_1$ is benzyl; W is carbonyl; U is NH; $R_3$ is (imidazol-4-yl)methyl; $R_6$ is cyclohexylmethyl; V is $SO_2$ and $R_{10}$ is isopropyl.

7. A compound according to Claim 2 wherein A is BocNH; $R_1$ is benzyl; W is carbonyl; U is NH; $R_3$ is (imidazol-4-yl)methyl; $R_6$ is cyclohexylmethyl; V is $CH_2$ and $R_{10}$ is isopropyl.

8. A compound according to Claim 3 wherein A is BocNH; $R_1$ is benzyl; W is carbonyl; U is NH; $R_3$ is isobutyl; $R_6$ is cyclohexylmethyl; $R_{13}$ is C=O, $R_{14}$ is $CF_2$; M is $SO_2$ and $R_{10}$ is isopropyl.

9. A compound according to Claim 3 wherein A is BocNH; $R_1$ is benzyl; W is carbonyl; U is NH; $R_3$ is pyrazol-3-ylmethyl; $R_6$ is cyclohexylmethyl; $R_{13}$ is

CHOH; $R_{14}$ is $CH_2$; M is NHC=O and $R_{10}$ is $CH_2CH_2$-isopropyl.

9. A compound according to Claim 4 wherein wherein A is 3,4-dihydroxypyrrolidinocarbonylamino; $R_1$ is benzyl; W is C=O; U is NH; $R_3$ is thiomethoxymethyl; $R_6$ is cyclohexylmethyl; P is hydrogen; and $R_{18}$ is sec-butyl.

10. A compound according to Claim 4 wherein wherein A is BocNH; $R_1$ is benzyl; W is C=O; U is NH; $R_3$ is thiomethoxymethyl; $R_6$ is 1,3-dithiolan-2-ylmethyl; P is hydrogen; and $R_{18}$ is sec-butyl.

11. A compound according to Claim 5 wherein A is 6-aminohexanoyl-NH; $R_1$ is benzyl; W is C=O; U is NH; $R_3$ is imidazol-4-ylmethyl; $R_6$ is cyclohexylmethyl; n is 0; T is methylidene; and $R_{12}$ is 3-methylbutyl.

12. A compound according to Claim 5 wherein A is BocNH; $R_1$ is benzyl; W is C=O; U is NH; $R_3$ is imidazol-4-ylmethyl; $R_6$ is cyclohexylmethyl; n is 1; S is OH; T is $ClCH_2$; and $R_{12}$ is isobutyl.

13. A pharmaceutical composition for treating renin-associated hypertension comprising a pharmaceutical carrier and a therapeutically effective amount of the compound of Claim 1.

14. A method of treating hypertension comprising administering to a host in need of such treatment a therapeutically effective amount of the compound of Claim 1.

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# INTERNATIONAL SEARCH REPORT

International Application No PCT/US87/00054

**I. CLASSIFICATION F SUBJECT MATTER** (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

US. CL. 514/17,18,19; 530/329,330,331
INT. CL. -4- A61K 37/43; CO7K 5/06,08,10; Co7K 7/06

**II. FIELDS SEARCHED**

Minimum Documentation Searched [4]

| Classification System | Classification Symbols |
|---|---|
| US | 514/17,18,19; 530/329,330,331 |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

**III. DOCUMENTS CONSIDERED TO BE RELEVANT** [14]

| Category * | Citation of Document, [16] with indication, where appropriate, of the relevant passages [17] | Relevant to Claim No. [18] |
|---|---|---|
| P,X | Chemical Abstract, Vol. 104, Issued 1986 abstract no. 88976x, (Matsueda) | 1-14 |
| P,X, | Chemical Abstract, Vol. 105, Issued 1986 abstract no. 43336t, (Luly) | 1-14 |
| P,X, | Chemical Abstract, Vol. 105, Issued 1986 abstract no. 433377u, (Luly) | 1-14 |
| P,X, | Chemical Abstract, Vol. 105, Issued 1986 abstract no. 24630, (Boger) | 1-14 |
| P,X, | Chemical Abstract, Vol. 105, Issued 1986 abstract no. 79375u, (Ryono) | 1-14 |
| P,X, | Chemical Abstract, Vol. 105, Issued 1986 abstract no. 60945h, (Fuhrer) | 1-14 |
| P,X, | Chemical Abstract, Vol. 105, Issued 1986 abstract no. 153525, (Thaisrivongs) | 1-14 |
| P,X, | Chemical Abstract, Vol. 105, Issued 1986 abstract no. 153529r, (Thaisrivongs) | 1-14 |

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

**IV. CERTIFICATION**

| Date of the Actual Completion of the International Search [2] | Date of Mailing of this International Search Report [2] |
|---|---|
| 17 March 1987 | 20 MAR 1987 |
| **International Searching Authority [1]** | **Signature of Authorized Officer [20]** |
| ISA/US | |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, [16] with indication, where appropriate, of the relevant passages [17] | Relevant to Claim No [18] |
|---|---|---|
| P,X, | Chemical Abstract, Vol. 105, Issued 1986, abstract no. 209389, (Iizuka) | 1-14 |
| A, | Chemical Abstract, Vol. 105, Issued 1986 abstract no.221487, (Ryono) | 1-15 |
| P,X, | Chemical Abstract, Vol. 105, Issued 1986 abstract no. 227324, (Sham) | 1-14 |
| P,X, | Chemical Abstract, Vol. 105, Issued 1986 abstract no. 191618, (Luly) | 1-14 |
| P,X, | Chemical Abstract, Vol. 105, Issued 1986 abstract no 115408, (Hester) | 1-14 |
| A, | Chemical Abstract, Vol. 105, Issued 1986 abstract no. 74762h, (Sawyer) | 1-14 |
| P,X, | Chemical Abstract, Vol. 104, Issued 1986 abstract no. 149415, (Boger) | 1-14 |
| A, | Chemical Abstract, Vol. 101, Issued 1984 abstract no. 163399, (Leckie) | 1-14 |
| X, | Chemical Abstract, Vol. 101, Issued 1984, abstract no. 125684m, (Rich) | 1-14 |
| P,X, | Chemical Abstract, Vol. 106, Issued 1987 abstract no. 33459s (Evans) | 1-14 |
| P,X, | Chemical Abstract, Vol. 106, Issued 1987 abstract no. 417y, (Toda) | 1-14 |
| P,X, | Chemical Abstract, Vol. 106, Issued 1987 abstract no. 19056, (Bueh) | 1-14 |
| P,X, | Chemical Abstract, Vol. 106, Issued 1987 abstract no. 5439s, (Ryono) | 1-14 |
| A, | Chemical Abstract, Vol. 103, Issued 1985 abstract no. 32110u, (Szelke) | 1-14 |
| X, | Chemical Abstract, Vol. 103, Issued 1985 abstract no. 156359, (Holladay) | 1-14 |
| X, | Chemical Abstract, Vol. 101, Issued 1984 abstract no. 86219, (Szelke) | 1-14 |
| X, | Chemical Abstract, Vol. 102, Issued 1985 abstract no. 91909) (Rich) | 1-14 |
| X, | Chemical Abstract, Vol. 102, Issued 1985 abstract no. 2468 (Veber) | 1-14 |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No |
|---|---|---|
| X | Chemical Abstract, Vol. 102, Issued 1985, abstract no. 181341, (Gelb) | 1-14 |
| X, | Chemical Abstract, Vol. 103, Issued 1985, abstract no. 160849, (Thaisrivongs) | 1-14 |
| X | Chemical Abstract, Vol. 103, Issued 1985, abstract no. 54459, (Szeke) | 1-14 |
| X, | Chemical Abstracy, Vol. 104, Issued 1986, abstract no. 162094b, (Dann) | 1-14 |
| A, | Chemical Abstract, Vol 104, Issued 1986, abstract no. 149414, (Boger) | 1-14 |
| P,X, | Chemical Abstract, Vol. 104, Issued 1986, abstract no. 149418, (Boger) | 1-14 |